Alberta Heritage Foundation
for Medical Research

# Functional diagnostic imaging in epilepsy

Paula Corabian, David Hailey

August 1998

HTA 10

# Functional diagnostic imaging in epilepsy

Paula Corabian, David Hailey

August 1998

This Health Technology Assessment Report has been prepared on the basis of available information of which the Foundation is aware from public literature and expert opinion, and attempts to be current to the date of publication. It has been externally reviewed. Additional information and comments relative to the Report are welcome, and should be sent to:

Director, Health Technology Assessment
Alberta Heritage Foundation for Medical Research
3125 Manulife Place, 10180 - 101 Street
Edmonton
Alberta T5J 3S4
CANADA

Tel: 403-423-5727, Fax: 403-429-3509

ISBN 1-896956-10-6

Alberta's health technology assessment program has been established under the Health Research Collaboration Agreement between the Alberta Heritage Foundation for Medical Research and the Alberta Health Ministry.

# Acknowledgements

The Alberta Heritage Foundation for Medical Research is most grateful to the following persons for their comments on the draft report and for provision of information. The views expressed in the final report are those of the Foundation.

Ms. Elizabeth Adams, Technology Assessment Program, Department of Veterans Affairs, Boston

Dr. M. Javidan, University of Alberta Hospital, Edmonton

Dr. Kenneth D. Laxer, Northern California Comprehensive Epilepsy Centre, San Francisco

Dr. Mary Anne Lee, Foothills Provincial General Hospital, Calgary

Dr. Devidas Menon, Institute of Pharmaco-Economics, Edmonton

Dr. José Conde Olasagasti, Agencia de Evaluación de Technologias Sanitarias, Madrid

# Contents

## Summary


- The functional diagnostic imaging (FDI) methods positron emission tomography (PET), magnetic resonance spectroscopy (MRS), functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) when used with MRI as magnetic source imaging (MSI) have all been considered as potential tools in the management of patients with medically refractory epilepsy (MRE).

- All are high cost technologies and their availability will be limited. They may be applied to many other conditions.

- In the clinical situation, all would be used as complementary techniques to anatomical imaging methods such as MRI, and would increase costs of management.

- The potential role of all these techniques in epilepsy would be in diagnosis and work-up of patients with MRE, who have no evidence of lesions on MRI or other anatomical imaging methods. Possibly 50 to 100 such patients per year in Alberta might benefit from use of FDI methods.

- MEG has been studied for many years as a method for use in epilepsy, but remains in the developmental stage with its clinical role yet to be defined.

- MRS provides unique information on cerebral metabolism but it is not established as a method in management of epilepsy.

- fMRI is a promising technology for application to epilepsy, but at this stage remains a research tool.

- PET has advantages over existing functional imaging methods in terms of accuracy of localization of lesions in patients with MRE. However, it has not yet been able to replace other technologies, and is not helpful for many patients with non-temporal lobe epilepsy.

- Of the FDI methods considered, only PET has a potential place in routine management of some epilepsy patients. Further work would be needed to define its role and economic costs and benefits.

# Introduction

This report has been prepared as part of a project to assess the role of high cost functional diagnostic imaging (FDI) and related methods in routine health care. In the present paper, the potential application of four FDI methods to the management of epilepsy is considered. The assessment considered the current status in this application of positron emission tomography (PET), magnetic resonance spectroscopy (MRS), functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) when used with MRI as magnetic source imaging (MSI). The aim has been to review available literature on the efficacy of each of the methods, and to provide preliminary discussion regarding potential cost and accessibility of these technologies.

Information on the FDI technologies is given in Table 1. Details of methodology used in the literature review are shown in Appendix A. The methodological quality of the primary studies included in the review was assessed in terms of the criteria formulated in Appendix B. Appendix C gives additional information about the FDI methods and Appendix D summarizes results of studies on their use in management of epilepsy. Some reference is also made in this report to single photon emission computed tomography (SPECT), a lower cost FDI method which is in widespread use in the investigation of persons with some forms of epilepsy.

The high cost FDI methods have had a long history. They have been used in medical research for many years, though technical developments continue. They provide a rich source of information about physiological function, and can be seen as complementary to those diagnostic imaging technologies which are used to assess anatomical details. The FDI methods can provide additional information about disease processes which may be helpful in developing and applying approaches to their management.

However, while these FDI methods have an established role in many areas of medical research, their place or potential application in routine health care is less clear. The FDI techniques are expensive and may also be demanding of scarce technical resources (57). There are issues related to the complexity, relevance and interpretation of the data they provide. Also, there is the question of the value of the additional information obtained through FDI to the management decision and subsequent health status of the patient.

From the perspectives of health technology assessment and the decision makers that it informs, a range of issues are relevant to the potential deployment of an FDI technique in routine health care. These will include:

- Technical performance of the FDI method.
- Incremental contribution to patient management (taking account of other methods that it may replace or supplement).
- Significance of the condition being investigated, in terms of population health and caseload.
- Incremental costs - taking account of costs of the FDI method, and the effect of its use on costs of other technologies.
- Access to the FDI method of those who would benefit from its use. FDI methods are versatile and applicable to many disease processes. Given their cost, they will continue to be scarce resources in health care. There will be claims from various clinical and research applications for time on the machine.

## Table 1: Comparison of functional diagnostic imaging technologies

| Technology | Basis of data | Spatial resolution | Temporal resolution | Advantages | Limitations |
|---|---|---|---|---|---|
| Positron emission tomography (PET) | measures changes in cerebral blood flow and energy metabolism caused by neuronal activity (measurement of radioactivity) | 4.5 -15 mm | seconds to minutes | • good spatial localization of active regions<br>• data can be analyzed qualitatively and quantitatively<br>• whole head coverage routine<br>• data may be overlayed onto CT or MRI<br>• can be applied to measure various abnormalities of cerebral functions (using different tracers) | • minimally invasive (requires radioisotope injection)<br>• experiments cannot be repeated frequently in a short period of time<br>• poor temporal resolution<br>• does not directly measure neuronal activity<br>• limited to interictal studies (prone to movement artifact)<br>• high cost *($2,000/scan in U.S.)*<br>• does not have capabilities to measure anatomy<br>• need for a cyclotron (on-site or located at relatively short distance) |
| Functional MRI (fMRI) | measures changes in cerebral blood flow and dynamics of brain oxygenation occurring within neuronal activity (measurement of radiofrequency signals) | ranges between "few mm" to "better than 1 mm" | 30 ms to 1 s | • high spatial and temporal resolution<br>• can be performed on available MRI equipment<br>• permits direct correlation of function with the underlying anatomy<br>• non-invasive (does not use ionizing radiation)<br>• several paradigms may be used within a single examination<br>• allows for repeated studies on individuals<br>• head and source model assumptions are not required (it is more direct than other FDI methods) | • does not directly measure neuronal activity<br>• cannot directly capture neuronal effects occurring on ms time frame<br>• spatial relationship between neuronal activity and observed changes not known<br>• signal changes are very small (1-12% at 1.5 T up to 25% at 4.0T)<br>• intensity of signal might be quite variable, even with constant stimulus intensities<br>• not a quantitative procedure (qualitative and relative nature of data)<br>• there is considerable potential for false positive and negative results<br>• patient cooperation is necessary during lateralization studies<br>• limited to interictal studies (prone to movement artifact)<br>• patients with pacemakers and magnetic implants must be excluded |
| Magnetic resonance spectroscopy (MRS) | measures changes in metabolite concentrations caused by neuronal activity (measurement of radiofrequency signals) | relatively poor ($1.7\ cm^3$) | seconds to minutes | • non-invasive<br>• high chemical specificity<br>• does not require sophisticated computer facilities (however, collection of data and subsequent data analysis require different systems than those used in imaging studies)<br>• can be performed with available MRI equipment | • does not directly measure neuronal activity<br>• most often spatial resolution is traded for chemical information (lower spatial resolution than that of imaging techniques)<br>• can reliably detect only molecules in millimolar concentrations<br>• time consuming<br>• limited to interictal studies (prone to movement artifact)<br>• patients with pacemakers and magnetic implants must be excluded |
| Magneto-encephalography (MEG) | measures the magnetic field generated by neuronal activity | within several mm (1- 8 mm) | ms | • non-invasive<br>• direct measurement of physiological regions of interest<br>• potential increased accuracy vs. EEG<br>• high temporal resolution of brain dynamics<br>• good spatio-temporal combination<br>• ease of examination | • high cost (requirement of magnetically shielded room)<br>• difficulty in spatial source localization (mathematical modeling errors)<br>• limited to interictal data (motion artifacts prone)<br>• depth and orientation limited (sensitive only to superficial tangential current sources)<br>• slowness of data acquisition<br>• dental work, steel surgical clips, pacemakers or other implants may intr magnetic artifacts |

EEG - electroencephalography; CT - computerized tomography; FDI - functional diagnostic imaging; MRI - magnetic resonance imaging; ms-milliseconds
PET- positron emission tomography; fMRI - functional MRI; MRS - magnetic resonance spectroscopy; MEG - magnetoencephalography;

## The nature of epilepsy

Epilepsy is a condition caused by sudden, brief changes in how the brain works. The physical changes are called epileptic seizures. A seizure occurs when there is an abnormal electrical discharge from a group of brain cells. The characteristics and frequency of seizures vary greatly. The type of seizure depends on the part of the brain where the discharge originates.

Epilepsy affects people of all ages and races. A large minority of patients with epilepsy (about 25%), despite available therapies with anti-epilepsy drugs, continue to experience seizures. (9;30) (21;40) They are referred to as medically refractory or intractable epilepsy patients. For those patients with focal onset, precise localization and surgical removal of the epileptogenic foci that cause medically refractory epilepsy (MRE) have been advocated in order to avoid progressive brain injury due to uncontrolled seizures and the adverse effects of anti-epilepsy drugs.

In Canada, epilepsy affects more than 1% of the population (more than 280,000 people). About 40% of these people have seizures that are not well controlled by medication (Epilepsy Canada, personal communication). Data on incidence rates for the Canadian population could not be located. A report dealing with management of epilepsy in the Australian population indicated that new cases of epilepsy could be expected to be in the range of 35 to 50 cases per 100,000 per year. (3) Incidence rates for MRE cases would be about 15 cases for 100,000 per year.

## Diagnostic investigations for presurgical evaluation of patients with medically refractory epilepsy

Most surgical candidates are MRE patients with complex partial seizures of temporal lobe origin. Presurgical evaluation of these patients is done to lateralize and localize the epileptogenic tissue that needs to be removed. Although epilepsy centres use different presurgical evaluation protocols, all utilize multiple diagnostic tests (including electrophysiologic, neuropsychologic and imaging techniques) to obtain converging lines of evidence on lateralization and localization of epileptogenic tissue.

Non-invasive interictal (between seizures) and/or ictal (during seizures) surface electroencephalography (EEG) is considered the standard procedure in this process. When seizure focus has not been conclusively located by non-invasive EEG, further monitoring using surgically implanted electrodes (invasive EEG) is required. However, invasive EEG techniques are associated with complications (e.g., intra-cranial infections, hemorrhage) and increased costs of presurgical evaluation. EEG examination is a lengthy process and some of its costs are associated with the significant length of stay required. The need for less invasive or non-invasive localizing techniques has led to the development and implementation of structural and functional diagnostic imaging in most epilepsy centres. (25;33;40;46;68;69)

Structural diagnostic imaging using magnetic resonance imaging (MRI) has become an essential part of the presurgical evaluation process, being useful in identifying lesions associated with epileptogenic region (structural lesions, mesial temporal sclerosis and hippocampal atrophy). MRI, particularly volumetric MRI, is preferred for patients with medically refractory temporal lobe epilepsy (MRTLE) since it can lateralize epileptic foci with accuracy in about 80% of surgical candidates (60% present evidence of hippocampal sclerosis and atrophy and 20% evidence of gross structural lesions). (25;33;39;40;46;60;65;95) However, subgroups of these patients have bilateral temporal lobe disease or multiple EEG foci that can not be identified on MRI. Most patients with ETLE are very difficult to lateralize or localize. (Javidan, personal communication).

The remaining 20% of these patients present no evidence of mass lesion (MRI scan is normal). In these cases, and in most cases with ETLE, different functional diagnostic imaging (FDI) techniques have been advocated to supplement and confirm surface EEG localization and lateralization. (32;36;65;68)

## Epilepsy in Alberta

Approximately 1% of the population of Alberta (about 29,000 people) suffer from a type of seizure disorder. Sixty to seventy five percent of the persons with epilepsy in Alberta (about 20,000) control their seizures with medication. About 30% (about 9,000) are resistant to medical therapy. Half of the MRE patients (about 4,500) would potentially benefit from surgery. Most of these (about 3,000) suffer from temporal lobe epilepsy (TLE). The role of FDI methods is in the management of patients with MRE who are potential candidates for surgery. (Javidan and Lee, personal communication).

In Alberta, epilepsy surgery is performed both in Edmonton and Calgary. In Edmonton, the Comprehensive Epilepsy Program is located at University of Alberta Hospitals. Approximately 100 to 140 cases (adult and pediatric) are evaluated per year. About half of these patients are admitted for diagnosis and the others for potential surgery. MRE patients are evaluated by non-invasive EEG recordings, MRI scan , ictal and interictal SPECT and neurosurgical assessment on phase I. MRI and SPECT are standard for all patients. The length of stay for monitoring is seven to 10 days for most adult patients. Some of the adults and many pediatric cases have short stay monitoring for one to three days. Approximately 25 patients have surgery for epilepsy every year at University of Alberta Hospitals (Javidan, personal communication).

In Calgary, approximately 100 potential candidates for epilepsy surgery are evaluated every year at the Alberta Children's Hospital and the Foothills Hospital. Inpatient EEG telemetry (using scalp electrodes and subdural strip electrodes where indicated), MRI, and neuropsychological testing are performed on all patients. SPECT has been in use at the Children's Hospital for some years and was recently introduced at the Foothills Hospital. At the Foothills Hospital most patients are admitted for a 5 day monitoring period and ideally seven days monitoring would be useful. Patients requiring more specialized evaluation, including fMRI and PET, are generally referred to the Montreal Neurological Institute or the University of Western Ontario. It is considered that, at present, only a small minority of patients who would benefit from these more

specialized evaluations end up being referred (3 or 4 patients a year). Epilepsy surgery is performed at both hospitals, and there are 20-25 cases per year (Lee, personal communication).

## FDI techniques

The use of FDI has been suggested for the work-up of epileptic patients to avoid, whenever possible, the use of invasive techniques for identification of epileptogenic foci. (66;69) In a commentary, Chugani suggests that FDI techniques are well suited for evaluation of epileptic patients since "epilepsy is primarily a functional disturbance of the brain". (16)

The FDI techniques have been used in studies to provide complementary information to that obtained by structural diagnostic imaging , rather than as a major method from which to make a presurgical decision. None of them has achieved supremacy in functional brain imaging because no one in isolation can adequately address the varied questions of interest. (1;73;94) Several reviews note that accurate definition of brain anatomy and the identification of structural abnormalities using MRI is necessary to adequately interpret data from all functional imaging studies. These include studies using PET, MEG, functional MRI and MRS in epilepsy patients. (1;26;27;45;94;95)

All noninvasive FDI techniques make their measurements from outside the head and infer locations of abnormalities within the brain. Hence, they must deal with the "inverse problem" (which is to estimate the cerebral source/sources underlying a signal measured extracranially) . In each case there is a measurement space, an image space and an algorithm that relates the two. The algorithm is used to reconstruct the events that occur in image space based on the measurements made outside the head. These estimates may or may not reflect a unique solution to the "inverse problem".

The physiological estimates localized by PET, fMRI and MRS are not direct measures of neuronal activity. They measure hemodynamic and metabolic changes caused by neuronal dysfunction. Many investigators believe that local neuronal activity in tissue is coupled to the local changes in metabolism, or blood flow. However, the precise relationship between these local changes is unknown. (1;73) Furthermore, changes in the hemodynamic response can refer to many different types of changes such as blood volume, blood flow, and blood oxygenation as measured by PET, or fMRI.

All FDI technologies considered for review are limited to interictal studies. There is still controversy on the reliability of presurgical localization of epileptic foci using interictal data (as an adequate alternative to ictal data) and on their prognostic value for determining surgical outcome. (32;37;42;55;70;73;77;81)

### *FDI techniques for MRE patients in Alberta*

At present, PET and MEG MRI spectroscopy are not yet available in Alberta. Functional MRI is used only for research purposes and is considered that, potentially, it is most useful feasible FDI technique for this indication since it could provide valuable

information and potentially replace the Wada test. A high magnetic field MRI unit (3T) will become available in Calgary within the next year and potentially could provide a resource for both MRI spectroscopy and fMRI of MRE cases. The only PET scan in Canada which is used extensively for evaluation of epilepsy is at the Montreal Neurological Institute (Lee and Javidan, personal communication).

## Indications of efficacy of FDI methods in epilepsy

There is a general difficulty in assessing the efficacy of FDI methods in epilepsy because of the limited scope and methodological quality of primary studies and the lack of systematic reviews. Most studies have been performed in patients with localized EEG data to "validate" imaging results and provide "confirmatory" evidence for localization and lateralization of the epileptic focus. (102)

## PET in epilepsy

PET has been used for more than 15 years to assist in the localization of epileptic foci during presurgical evaluation of MRE patients. Changes in cerebral blood flow and particularly glucose metabolism have been used to identify epileptic foci in an attempt to reduce the need for more invasive techniques. Reviews of earlier studies mention that PET imaging of interictal cerebral metabolism has been shown to be more sensitive than interictal PET measurement of cerebral blood flow (CBF) in MRTLE patients. (27;66;69;73;94;95) Data from 32 TLE patients who have had surgery suggest that interictal CBF measurements using $^{15}O$-labelled water PET studies are unreliable and "should not be used to help select patients for temporal lobectomy." (100;101) On the other hand, Theodore (100) suggests that interictal PET CBF studies "are becoming very useful for presurgical cognitive mapping and may be able to replace the intracarotid amytal test for language and memory lateralization." (100)

Interictal PET imaging of cerebral metabolism can be analyzed qualitatively and quantitatively (usually expressed as asymmetry for measurements in defined regions of interest). Glucose metabolism is the most commonly measured parameter, using 18F-FDG (18F-fluorodeoxyglucose, a glucose analogue). There is controversy on whether to use qualitative analysis rather than quantitative analysis of FDG PET findings. (1;27;66)

Based on the assumption that, between seizures, the hypometabolism zone involves the epileptogenic zone, FDG PET has been applied and advocated to confirm EEG localization and lateralization of epileptogenic foci, for selecting surgical resection locations in children without EEG localizations, to define cerebral areas for intra-cranial EEG study, to asses functional integrity in children and adults prior to epilepsy surgery and for functional mapping of cerebral function. (16;73;94) However, uncertainty remains as to the relation between PET metabolic findings in the interictal state and the epileptogenic region since there is evidence to suggest functional and biochemical heterogeneity within the interictal hypometabolic area. (16;65;66;73;100)

Reported results of FDG PET measurement of cerebral metabolic rate in MRE patients clearly differ for temporal and extratemporal locations of epileptogenesis. Temporal lobe hypometabolism measurements were highly correlated with temporal lobe EEG

abnormalities, but extratemporal demonstration of reduced cerebral metabolic rate by PET was more often discordant with EEG findings. The reviewed literature showed that the incidence of focal hypometabolism in TLE patients varies between 60% to 93% (22;58;72) (Table 3), and between 45% and 60% in patients with neocortical frontal lobe epilepsy (FLE) (27;60) (Table 3). Differences in PET imaging technology, data analysis and patient selection may explain, in part, the variation in results.

The evaluation of the clinical utility of FDG PET has focused on TLE patients. Interictal PET has been shown to be less valuable in the evaluation of ETLE patients, particularly in cases with normal MRI and non-focal EEG, (22;27;55;60;73;94) (Table 3). Most ETLE patients have no focal MRI abnormalities. (19;23) Regardless of the monitoring technique used, the likelihood of confident EEG localization of seizure onset and a subsequent surgical cure in these patients is significantly less than that obtained in those with TLE. (84) Hypometabolism is rarely found in patients with FLE who have normal MRI scans and when present it may be potentially misleading with regards to the site of the seizure onset. (60;84) PET appears to be helpful only in a small proportion of non-lesional ETLE pediatric cases (particularly in children with intractable infantile spasms and focal features on EEG). (16;17;84) It has also been suggested that PET may help direct the electrode implantation in ETLE patients requiring invasive EEG. (60)

It has been reported that PET provides needed information in pediatric MRE and many other childhood seizure disorders (infantile spasms, Lennos-Gastaut syndrome, Sturge-Weber syndrome, brain malformations). (16;55;74;88) Many investigators consider that PET can play a significant role in managing children with seizure disorders potentially reducing the morbidity and costs associated with long-term care of patients who would otherwise remain untreated. However, PET must still be used in conjunction with structural imaging (computerized tomography or MRI) and EEG when identifying surgical candidates. (16;88)

Potential clinical indications for PET in pediatric epilepsy include

- patients with MRE, being considered for surgery, for whom MRI or CT fails to show a lesion (PET localization and lateralization to avoid invasive techniques);
- medically refractory patients considered to have cryptogenic infantile spasms following extensive evaluation (PET may provide additional information);
- patients considered as surgery candidates whose EEG suggests multifocal epileptogenicity (PET may confirm presence of multiple focal abnormalities; by correlating PET findings with EEG, withdrawal from surgery or use PET findings to guide placement of intra-cranial electrodes may be considered);
- patients with extensive unilateral lesions being considered for hemispherectomy (PET may provide an assessment of the functional integrity of the normal hemisphere). (16;55;88;94)

Several commentaries and reviews suggest that when scalp EEG and FDG PET findings correlate, video EEG monitoring and invasive EEG may be unnecessary to localize the epileptogenic foci in TLE patients before surgery. (13;40;60;88;102;106) It has also been reported that FDG PET is most beneficial when used in the context of total presurgical

evaluation of epilepsy patients, including scalp EEG, invasive EEG, neuropsychologic testing, and structural imaging. (7;74;94)

FDG PET is a complementary tool rather than a substitute for EEG. Sensitivity and positive predictive value for FDG PET are highest in TLE. The finding of regional brain hypometabolism is not specific for epilepsy and correlation with EEG is necessary for planning epilepsy surgery. (13;27) Also, the area of hypometabolism frequently exceeds the area of involvement predicted either by surface or invasive EEG. (73;94)

Several authors have suggested that FDG PET can compliment but does not supplant systems that image anatomy (27;56;74;104). It has been suggested that FDG PET is the FDI procedure of choice in MRTLE patients without lateralizing MRI data. (32;55) In patients with mesial temporal foci, who have an abnormal hippocampus on MRI concordant with ictal EEG, PET does not provide any new information and is of little use (60;73) (Javidan, personal communication)

### *Comparison with other diagnostic methods*

In the literature reviewed for this report, PET is considered to be superior to SPECT (in terms of image quality and quantification of radioactivity) for interictal studies. At present. It appears to be more sensitive than qualitative MRI in most studies of patients with complex partial seizures of temporal origin. (14;16;22;27;44;84;94) However, direct comparison between various imaging techniques is limited because of small patient populations present in most studies and the technical advances that continue to be made. (27;60)

A literature review, in which these techniques were examined individually with regard to their reported ability to predict epileptogenic zone defined by EEG, provided comparative data on their diagnostic accuracy. (94) Patients were divided into those with temporal and extratemporal epilepsy and the results of MRI, interictal and ictal SPECT and PET in patients who also had EEG reported were analyzed. Findings from this review are summarized in Table 2.

## Table 2: Comparative data on the diagnostic accuracy of PET, SPECT and MRI as judged by EEG

| Technique (patient numbers) | Temporal localization (patient numbers) | Extratemporal localization (patient numbers) |
|---|---|---|
| interictal FDG PET<br>(n = 312; unlocalizing or negative in 75/312) | (n= 205)<br>Sensitivity: 84%<br>Specificity: 86% | (n= 32)<br>Sensitivity: 33%<br>Specificity: 95% |
| interictal SPECT<br>(n = 539; unlocalizing in 183/539) | (n= 291)<br>Sensitivity: 66%<br>Specificity: 68% | (n= 65)<br>Sensitivity: 60%<br>Specificity: 93% |
| ictal SPECT<br>(n = 108; unlocalizing in 12/108) | (n= 80)<br>Sensitivity: 90%<br>Specificity: 77% | (n= 16)<br>Sensitivity: 81%<br>Specificity: 93% |
| MRI<br>(n = 809; unlocalizing or negative in 366/809) | (n= 370)<br>Sensitivity: 55%<br>Specificity: 78% | (n= 73)<br>Sensitivity: 43%<br>Specificity: 95% |

Source: Reference (94)

Menzel et al. (73) reviewed reported data on 1,300 epilepsy cases to determine the relative contribution of FDG PET (interictal measurement of glucose metabolism) versus SPECT (interictal and ictal measurement of regional CBF) to the presurgical evaluation process. In considering the number of correctly identified areas of abnormal metabolism or perfusion, these authors found a comparable sensitivity of FDG PET (71% of all 352 cases) and interictal SPECT (62.4% of all 674 cases). Ictal SPECT showed a sensitivity of 87% of all 259 cases.

Some evidence suggests that interictal PET and interictal SPECT have statistically similar seizure focus localization capabilities (for correct localization, $p=0.999$ and for incorrect localization, $p=0.625$) when directly compared in individual patients. When patients with evidence of mass lesion on MRI are excluded the positive predictive values (PPVs) of interictal PET and SPECT are comparable, but overall the PPV of PET is greater. (69)

Spencer et al. suggest that PET measurement of the metabolic rate is more useful for confirming or demonstrating localization of epileptogenic focus than is measurement of cerebral blood flow by interictal SPECT. (94;95)

Ictal SPECT appears to offer good sensitivity and specificity for TLE, both comparable with those of interictal PET. It has also been shown to be more useful than PET in ETLE.

(27;40;55;60;68;73;94) However, its availability is limited by the requirement for immediate injection of the radio-nuclide tracer at the onset of seizure activity. (39;60;73;94)

Recently, quantitative MRI techniques for measurement of hippocampal formation (HF) volume (referred to as volumetric MRI or MRI volumetry) have been reported to correctly lateralize areas of structural abnormalities in temporal lobes in 63%-90% of cases, with sensitivity and specificity of 100% when mesial temporal sclerosis was present. (16;46;50;72) Gaillard et al. (35) compared FDG PET and volumetric MRI in 18 adult patients with complex partial epilepsy in whom the ictal focus was identified by video-telemetry EEG. They found a significant correlation between HF volume and assymetry index for inferior mesial and lateral temporal lobe metabolic rate of glucose ($p<0.01$). The investigators concluded that "PET is more sensitive than MRI volumetry in identifying ictal focus but does not provide additional information when HF atrophy is present." (35)

These results have been confirmed by Knowlton et al. (52) who conducted a prospective study to compare the performance of FDG-PET, MRI-based hippocampal volumetry (HV) and proton MRSI in EEG-defined unilateral TLE, with no evidence of lesions on diagnostic MRI. Comparison was possible in 23/25 patients included in the study. FDG-PET lateralized in 87% of these patients, HV in 65% and proton MRSI in 61%. Combined HV and proton MRSI results lateralized 83% of the patients, a value comparable to that of FDG-PET. Based on these results, the investigators recommended the selective use of FDG-PET in the presurgical evaluation of patients with EEG-defined TLE. Their data suggest that although "FDG-PET remains the most sensitive imaging method to correlate with EEG-lateralized TLE", "for patients with hippocampal atrophy, PET provides essentially no new lateralization or outcome information".

### *Practical details*

As with other FDI techniques, the patient must remain quiet and still during PET examination to avoid producing movement artifacts. Cerebral images of glucose distribution are averaged over a period of 30 to 40 minutes and, although they are weighted to the initial few minutes after injection, are more correctly interpreted under steady-state conditions. (60;73;94) For this reason and because of the logistic difficulties of making short-lived radio-isotopes available at the unpredictable times of epileptic seizures, PET studies are usually performed in the periods between seizures (interictally). Also, the long time required for F-18-FDG phosphorylation in the brain (about 45 minutes) does not allow the study of rapid changes of function which occur during seizures. (73;74)

PET evaluation of glucose metabolism in epileptic children is often difficult. Normative data with FDG PET in children are limited, most individuals have a history of therapy with anti-epileptic drugs that are known to alter global glucose metabolism, and sedation is needed. (14;35;36;74) Sedation is a problem because drugs used to sedate young patients have variable effects on global brain metabolism and blood flow and their effects on regional values are not well known. It has been suggested that sedatives be administered after the FDG uptake phase is completed or else avoided. (74)

In infants younger than 1 year of age, when cerebral glucose metabolic rates are relatively low, differentiation between normal and abnormal areas of glucose metabolism may be impossible to appreciate by visual analysis of PET findings alone. (17)

PET is sensitive to technical details. False positive FDG PET scans have been attributed to previous depth electrode implants, improper positioning, unrecognized ictal activity when EEG monitoring is not performed, and over-interpretation of images on purely visual analysis. (1;27;94;100) Visual interpretation of FDG PET findings is limited by the fact that the region of hypometabolism may be extensive and by structural changes associated with epilepsy. Although it usually includes the epileptogenic zone as defined by EEG or histopathology, the functional disturbance involves a greater area of tissue (which may be multifocal as well as regional). (16;22;27;36;47;65;66;94) It has been suggested that focal cerebral atrophy, neoplasms and areas of cortical dysplasia may influence the visual interpretation of the functional images. (60) It is uncertain whether PET can distinguish between mesial and lateral temporal seizure onset. (100;102)

Henry et al. (47) evaluated interpretation replicability of interictal FDG PET scans in 241 MRE patients obtained with three different tomographs. They reported frequent disagreements in scan interpretation between two neurologists with prior experience in reading PET results, and best replicability with the highest performance tomograph. Replicability of "unbiased interpretations in detecting regional hypometabolism" was characterized as "adequate" for clinical application of interictal FDG PET studies performed with any of the tomographs.

## MRS in epilepsy

At present, it is generally considered that MRS is predominantly a research diagnostic tool that holds great clinical potential. (10;20;21;81) Similar opinion was current at the time of the first health technology assessment dealing with this technology, fourteen years ago. (78) According to the present literature reviewed for assessment, one area in which it has been shown to have innovative potential is the presurgical evaluation of MRE patients.

Both proton and phosphorus MRS studies have been performed in MRE patients referred for surgery. However, most studies have used proton MRS, because it can be performed with the existing MRI equipment, whereas phosphorus MRS requires utilization of special head coils. In addition, hydrogen nuclei have a higher MR sensitivity than phosphorus nuclei and the metabolites of interest in proton studies are more abundant than phosphorus compounds. Therefore, spatial resolution is superior in proton spectroscopy.

### *Proton MRS*

A typical proton spectrum in a normal brain shows a series of peaks usually defined as originating from N-acetyl-aspartate (NAA) (a constituent of functioning nerve cells), creatine-phosphocreatine (Cr-PCr) and choline (Cho). The latter are used as reference compounds as their levels are relatively constant. (10;20;26)

Most proton MRS studies on epilepsy have been on MRTLE patients during interictal periods. The characteristic MRS abnormality is a relative reduction in the concentration of NAA, usually interpreted as reflecting a reduction in neuronal activity (loss or dysfunction of neurons). Investigations also reported increases in Cho and Cr signal intensities in these patients.

Based on the assumption that there is decreased neuronal density in the epileptogenic zone and that NAA is associated with neuron density, it has been hypothesized that MRS may detect the epileptogenic lobe by showing a decreased NAA signal in the epileptogenic area. However, the mechanism of the reduction of NAA in TLE patients is not well understood. (21;65) It has been suggested that some of the observed NAA decrease may be due to tissue loss rather than selective neuronal loss. (40) Also, published results of studies involving healthy volunteers suggest that regional NAA decreases may be observed in the temporal lobes of normal individuals. (21) (Table 4)

Bilateral spectral abnormalities (decrease in NAA concentrations and NAA/Cr+Cho ratio) have been observed in 20%-50% of reported TLE cases. (19;23;24;29;39;40;59) It has been suggested that the observed bilateral MRS abnormalities may be associated with and possibly responsible for poor surgical outcome. (29) However, the significance of bilateral abnormalities is poorly understood and it is not clear how they may affect the surgical outcome. (19;52)

Quantification of signals is a critical issue in MRS. Most authors have used semi-quantitative approaches based on metabolite ratios. (39;40;66) The most sensitive measure for epileptogenic zone lateralization in concordance with EEG was the NAA/(Cr+Cho) ratio. (24;29)

In addition to NAA, Cr, and Cho peaks, visualized with interictal proton MRS studies, some investigators documented presence of elevated lactate following complex partial seizures (post-ictally) in TLE and ETLE patients. Increase in lactate remained confined to small regions within the epileptogenic zone and persisted for up to 7 hours. (39;40;59;80)

Proton MRS has been reported to be extremely sensitive (88 % to 100% sensitivity at magnetic fields 1.5T or higher) in the detection of unilateral and bilateral metabolic abnormalities in patients with TLE. (39;40;54;59) (Table 4) It has also been reported that proton MRS may be used for localizing epileptogenic regions in all partial epilepsy patients (MRS has been shown to detect decreased NAA within epileptogenic region in FLE patients). (39;40;59)
Some investigators suggest that MRI and proton MRS provide complementary information since MRS provides evidence of more diffuse abnormalities that extend beyond the focal lesions demonstrated by MRI. (19;23;34;59)

A major limitation of current proton MRS techniques is interference from water and lipid signals. The techniques used to minimize this interference limit brain regions that can be analyzed. (26;39;40;59)

### *Phosphorus MRS*

Phosphorus MRS studies typically measure high energy phosphate compounds. These include inorganic phosphate (Pi), phosphomonoesters (PME), phosphodiesters (PDE), phosphocreatine (PCr) and adenosine triphosphate (ATP). Estimate are also made of cerebral pH. Abnormalities that have been associated with epileptogenic areas include increased Pi (only in TLE patients), reduced PME and increased pH (in both TLE and ETLE cases).

A major limitation of this procedure is that it uses a large effective voxel size due to the low concentrations of the metabolites. Also, the adjacent peaks may overlap, making the spectral analysis difficult, and results may vary considerably depending on the method of analysis. The assessment of pH (dependent on chemical shift rather than the measured integral for a peak) is considered by some investigators as the most reliable phosphorus MRS measure in both TLE and ETLE patients. (39;40)
Preliminary studies have suggested that interictal phosphorus MRS may be helpful in defining the epileptogenic region in the presurgical evaluation of TLE and ETLE patients. (26;39;40) However, it is not clear yet whether phosphorus MRS provides useful localization and lateralization information over and above that available from high resolution MRI. All reports localized for this review conclude that future studies are needed to compare phosphorus MRS with high resolution MRI.

### *MRS as an FDI technique for epilepsy: indications of efficacy*

MRS studies in epilepsy have commonly been based on examination of single voxels. More recently, there have been studies which have used simultaneous assessment of signals from multiple voxels, a technique that permits spectroscopic imaging (MRSI) also called chemical shift imaging. MRSI utilizes phase encoding to localize voxels and allows acquisition of spectra simultaneously from multiple regions within the area in which the water signal has been suppressed. Spectroscopic data are displayed in an image format similar to that for MRI, providing a direct visual correlation between metabolic levels and anatomy.

MRSI has been reported in various reviews and commentaries to be a promising adjunctive tool for the presurgical evaluation of epileptic patients. (26;29;39;40;59;60) Several investigators reported agreement between proton MRSI and EEG localization in 83% to 90% of TLE patients. (11;12;79) However, MRSI is still in its infancy. It is too time consuming and prone to artifacts (more so than a single voxel method) to be applicable in a patient examination on a routine basis. (21;26;27;29;82)

The reviewed literature suggests that MRS adds confirmatory diagnostic information concerning the lateralization and localization of the seizure foci in MRE patients. It has been suggested that such information may reduce the hospitalization period and the need for invasive techniques. (19-22;26;33;34;39;59;65) Results reported by Knowlton et al. suggest that in TLE patients with normal MRI, adding a proton MRSI to the presurgical MR protocols (52) can approach PET sensitivity for lateralization. The investigators consider that this additional sequence during an MRI should eliminate the need for PET "when other imaging or clinical findings are equivocal". However, most

investigators consider that further studies, with larger sample size, are needed to assess validity and reliability of MRS in the presurgical evaluation of epilepsy patients.

There are still unanswered questions

- how does it compare with other non-invasive diagnostic methods ?
- how does it relate to the most recent MRI techniques, shown to be very useful at least in TLE patients? what is the reliability of MRS in ETLE patients?
- what is the probability that it will replace invasive EEG?
- what is the significance of bilateral abnormalities as defined by MRS? Do they affect the surgical outcome ?

There are also some technical problems that remain to be solved:

- the need for magnets of higher field strength to improve spatial resolution;
- availability of pulse sequences and software permitting exploration of the entire brain rather than selected volumes and slices;
- creation of software permitting a technologist to operate the machine for routine studies;
- need for stringent control of technical aspects of the procedure. (20;26;27;54;80)

## Functional MRI in epilepsy

Several preliminary studies provided support for the use of fMRI in the presurgical evaluation of MRE patients. These studies suggest that fMRI has three potential roles: localization of seizure foci, lateralization of language (and possibly memory) to one hemisphere before potential surgery and to localize functional (eloquent) cortex before surgical resection of the seizure foci. (8;58)

Preliminary results (from case reports) demonstrated that functional MRI may be a useful tool in the identification of seizure focus in epileptic patients. However, it is considered that further investigations are needed to assess its validity and reliability. (8;54;58)

The reviewed literature suggests that fMRI holds great promise for replacing several invasive and costly diagnostic procedures (invasive EEG monitoring, Wada test, videotelemetry, and direct cortical stimulation mapping). However, at present fMRI as a diagnostic tool in epilepsy is still in its infancy and cannot be used to replace any invasive procedures. (1;8;33;54;83) More work needs to be done, particularly in paradigm development and validation . Other problems include difficulty in obtaining concurrent EEG and in recording spontaneous seizures while the patient is in the magnet. (8)

If fMRI can be proven to reliably predict language dominance, some patients with epilepsy could potentially forego the Wada test (which is invasive, limited in interpretation and fallible (Javidan, personal communication) (109) in their presurgical examination. Epilepsy centres perform the Wada test (reported by patients to be a very stressful procedure) to determine language laterality, but many also use it to determine memory lateralization. Several investigators have used fMRI to determine language

lateralization (using various language paradigms, especially word generation ) in small series of patients with epilepsy (very few with atypical language organization) and reported promising results. (8;27) Little research using fMRI has demonstrated hippocampal function in normal brain during memory processing. (8;48) However, fMRI applications of memory mapping in epilepsy are still lacking. (8) Also, it is not yet known whether suitable paradigms can be developed to lateralize memory functions satisfactorily. (27) In order to replace Wada test, fMRI must be able to lateralize language as well as memory.

To date only a few cases have been reported in which fMRI was used in epileptic patients for intra-hemispheric functional mapping (to localize eloquent cortex). Functional MRI has been used so far to confirm localization of function by some other techniques. (8)

The reviewed literature suggests that fMRI is a promising technology whose place is not yet established. (14;41;48;56;61;81;108) It has potential to become more widely used than SPECT and PET, also used to detect metabolic and hemodynamic responses to neuronal activity. (22;41;81)

A number of biologic phenomena that can affect fMRI findings still remain to be adequately addressed. These include: uncertainty about the mechanism of the detected signal change; uncertainty about the optimal task for activation of specific cortical regions; and uncertainty about draining veins/in-flow effects. (48;56)

Technical problems that remain to be solved include

- signal optimization in different tasks;
- uncertainty about the optimal magnetic field strength;
- sensitivity to patient motion and subject handling (Use of some physical restraints may be contraindicated in epileptic patients, (62) and need for stringent head-motion control limits the choice of subject responses available for measurement; (18)
- artifacts produced by physiological noise (respiration, cardiac pulsation and brain pulsation);
- lack of compliance with requirements;
- difficulty in defining consistent regions of interest for analysis; and
- quantitative detection of signal changes. (1;18;48;56;58;61;62;75;105)

## MEG/MSI in epilepsy

The magnetic source imaging (MSI) method combines MRI with magnetoencephalography (MEG) to enable anatomic localization of MEG recordings on the patient's MRI scan. Varous computer reconstruction techniques have been used in attempts to provide a graphic representation of the spatial relationship between brain structure, function and pathology information. (2;37;53;64;67;76;81;87;90)

There appear to be no reports of controlled studies conducted to determine whether and for what clinical conditions MEG can contribute significantly to the efficacy and cost-

effectiveness of evaluation of patients suffering from neurological, neuro-surgical and/or psychiatric disorders. Most clinical research in MEG has occurred in localization of epileptogenic cortex in patients with medically intractable partial seizure referred for surgery. The reviewed literature suggests that one of MEG's potential applications is for localization of the seizure focus in MRE and for classifying patients with mesial versus lateral temporal lobe epilepsy. (15;28;37;64;67;87;103).

Although MEG has been developed primarily as a method for investigation of seizures, it has not been adequately evaluated to determine its clinical utility in epilepsy. (5;22;37;103) Its use and efficacy have been reported only by case studies. Reports of these studies (Table 5) suggest that MEG alone or in combination with other techniques (MRI, fMRI, EEG) has provided promising results. These have demonstrated the capability for localization of epileptic foci (to localize foci in partial epilepsy, to focus depth electrodes for presurgical evaluation of intractable epilepsy and to compare epileptic activity). MEG can also locate the central sulcus (beneficial in that it allows for pre-operative planning).

It has been suggested that MEG may equal the accuracy of electrocorticography providing an alternative to invasive monitoring in the localization of superficial epileptic foci. (22;37;53;98) Published case series suggest that the use of MEG in presurgical investigation may result in a reduction of invasive recordings, provision of useful guidance for invasive functional mapping and additional information concerning spatial relation of focus, lesion and functional zone. (15;37;38;53;97;99)

Some evidence suggests that MEG appears promising in the evaluation and surgical management of non-lesional convexity epileptic foci if surgical outcome is used as an index of localization accuracy. (93) In cases with orbitofrontal epileptic foci MEG has limited value in the surgical planning (Table 5).

During MEG examination, the patient has to stay immobile, to avoid generation of movement artifacts. (28;64;71;107) Despite the advances in MEG technology and data analysis procedures, it cannot be used to measure brain activity in epileptic patients during major motor seizures or in uncooperative subjects. (28;64;71) Its application to epilepsy is mostly limited to the assessment of discharges occurring between seizures. (63;64;70;81) Several investigators suggest that MEG interictal data may be adequate for planning and management of ablative epilepsy surgery. (81;85;87) (Table 5)

According to the reviewed literature, a final decision on the value of MEG technique for routine diagnosis is not yet possible. Accuracy of dipole localization with MEG continues to be refined. However, the validity of using dipole localization, particularly from interictal data alone, has not been established. The clinical application of MEG in epilepsy has yet to be defined by comparing MEG data with non-invasive and invasive EEG data.

## Methodological quality of primary studies included in the review

In the reviewed literature, the widely credited role of FDI techniques is that of increasing diagnostic certainty regarding the need for invasive procedures. However, the reported studies on the use of PET, MRS, and MSI in epilepsy are methodologically weak and tend to overestimate the accuracy and clinical value of these techniques. At present, there are no published randomized controlled trials conducted to evaluate the diagnostic accuracy and impact of these techniques. None of the reviewed studies clearly met all the criteria for methodological quality formulated in Appendix B (see comments in Tables 3, 4, and 5).

The reviewed literature is limited in several respects and subject to different biases. Studies that compared PET/MRS/MSI to other diagnostic techniques did not randomize the order of test administration (hence they may be subject to context bias). In many cases, the result of one test led to the decision to confirm localization and lateralization of epileptic foci by using the assessed test (hence, they are assumed to be subject to work-up bias).

Another shortcoming is the lack of epidemiologic information in the published studies conducted to assess the diagnostic accuracy of the reviewed FDI techniques. Patient selection and eligibility criteria are often inadequately described. The studies generally enrolled carefully selected patients and the source of the patient cohort was not clearly specified (hence they may be subject to selection bias) Most studies included relatively small numbers of patients and did not include control groups (to account for biologic variation in test results or differential diagnostic with other conditions).

Differences between the results from the reviewed studies may be influenced by different approaches to methodology of region of interest (ROI) placement, different data analysis strategies, and by different reference standard methods used to determine the location of epileptogenic foci. For example, non-invasive EEG, invasive EEG, and post-surgical outcome ( also defined differently) have all been used for reference purposes. Performance of the assessed test differed from one study to another. There were differences in instruments (with different spatial resolutions), methods used to reconstruct the images, and in post-processing methods. Different hardware and software were used for data analysis and co-registration with MRI. When findings were visually interpreted, the adequacy of blinding (when the interpreters were blind to the other methods) was not analyzed and issues of inter-observer variations were not addressed.

The reviewed studies tended to give inadequate details about what happened to patients whose FDI results did not accurately reflect their disease status. Few studies discussed the potential or actual changes in treatment that resulted from incorporating the assessed FDI technique into presurgical evaluation at critical decision points.

Patients usually underwent surgical treatment primarily on the basis of EEG lateralization and localization of the seizure focus. The assessed FDI technique was usually employed to confirm the EEG findings, in conjunction with MRI and other tests. Consequently, the intrinsic value of the FDI method for the assessment of seizures and

influencing patients management and outcome could not be evaluated. In most cases it has been used to refine information already available from other functional or structural imaging technologies. The assessed FDI method has been used as a complementary investigation and not as a major criterion on which to make a presurgical decision.

Overall, the reviewed literature includes a number of studies on technical performance of the FDI methods, which are helpful though of limited quality. Only poor quality evidence is available on the influence of the FDI methods on patient management and eventual outcomes.

## Cost and access considerations

In principle, issues of cost and access are important for all FDI technologies. However, on the basis of the information obtained from the literature review, only PET is worth considering in terms of routine health services in Alberta at this stage. MRS, fMRI and MSI remain developmental and are not realistic options in management of MRE either in Alberta or for out of province referral.

There is a general lack of relevant data on cost and access. The following points give indications of analyses which would need to be undertaken.

The cost of a PET examination in Alberta is uncertain, and would depend, among other things, on the specifications of the installation that was put in place. However, on the basis of information on charges for PET services in other countries, the cost of an examination of a patient with MRE using the technology could be of the order of $2,000. The available literature suggests that this cost would be additional to those of other diagnostic imaging methods used in the management of such patients. There is no indication that PET would be able to replace these other methods. However, there is potential to replace some electrophysiology investigations, though the extent of such substitution in routine care is still unclear. Overall, there would be the expectation of a significant increase in costs of investigations for this category of patient.

These additional costs then have to be put in context. Use of PET in this application would provide additional information on patients with MRE who present particular difficulties in diagnosis and management. If the additional information made a substantial difference to management decisions in a number of cases, PET could be a cost saving technology. There would be the potential for more accurate localization of epileptogenic region providing an additional guide to surgery and possibly better patient outcomes. In addition, in some cases, the use of PET might provide information to rule out use of interventions which would be inappropriate. Use of additional imaging technology has the potential to reduce hospital stay for this patient group.

At this stage, none of these propositions has been proved. Projections of cost for MRI in epilepsy have suggested that the technology has provided cost savings. (4) Similar arguments might apply for PET, where applied appropriately to a patient group which is at a particular need, but the case still needs to be established. The impact of PET on costs and outcomes would depend on availability of both appropriate patient selection

criteria and of effective interventions. No data are available at this stage on the impact of PET on overall management of MRE patients or on their eventual health status.

Information from the centres in Edmonton and Calgary which undertake epilepsy surgery suggests that perhaps 200 persons per year are evaluated for potential surgery. About two thirds of these would have TLE. The majority of TLE cases - perhaps 70% - could be managed with use of MRI, and FDI methods would not be required. About 40 TLE cases per year might therefore benefit from FDI investigations.

MRI would not be helpful for the remaining 70 patients per year with MRE. In these cases, FDI methods might have a role. However, the information available for this report suggests that in many cases, PET cannot locate epileptogenic sites in ETLE, so that its value in this application remains uncertain. On the basis of the current caseload in Calgary and Edmonton, perhaps 50 cases per year might benefit from PET examination. There is some unmet demand for investigation of epilepsy cases (Javidan and Lee, personal communications) so that the number of MRE cases that might benefit from use of PET in Alberta could perhaps be 100 per year.

PET is expected to remain a scarce resource in the province and there would undoubtedly be competition for time on the machine between users. Availability of this examination for patients with MRE would depend on a number of factors, including the scanning protocol used, overall patient throughput, hours of operation of the facility, and competition for instrument time from other clinical and research areas.

## Discussion

All FDI methods considered in this report offer additional information to that available from other diagnostic methods. They potentially have a useful place in routine health care, in addition to their established roles in medical research. However, even after many years of research and development, that potential remains unfulfilled. For the application considered here, management of epilepsy, MRS, fMRI and MEG remain in the research and development stage.

The situation with PET seems somewhat different, and use of this method in assessment of appropriately selected patients with MRE is an option that might be considered. There is evidence that PET offers advantages over other imaging methods in MRE in terms of sensitivity and specificity. Possibly, use of PET could provide benefits in a small minority of patients with epilepsy whose management presents particular difficulty.

However, substantial uncertainty remains regarding the use of PET in this application. The quality of the available evidence on its performance and impact is limited. PET has not yet been shown to be capable of replacing invasive EEG methods, and there is little information regarding its impact on patient management decisions and eventual outcome. Economic costs and benefits of the method in the context of Alberta health care are unknown.

It is suggested that any use of PET in the management of Alberta patients with MRE should be in the context of well designed studies to evaluate clinical and economic impact of the technology.

# Appendix A : Methodology

A literature search for articles published between 1993 and November 1997 which reported studies on human subjects was conducted. Sources of information included EMBASE, MEDLINE, HealthSTAR and ECRI's database. The literature search was kept updated during the review.

The words 'epilepsy', 'magnetic resonance imaging', 'tomography, emission-computed', 'positron emission tomography', 'nuclear magnetic resonance', 'magnetoencephalography', 'diagnostic imaging', 'economic aspect' were used as subject headings.

Key text words and phrases such as 'functional imaging', 'positron emission tomography', 'PET', 'functional magnetic resonance imaging', 'functional MRI', 'FMRI', 'functional adj1 (mri or magnetic resonance imaging)', 'magnetic resonance spectroscopy', 'MRS', 'neurology', 'brain', 'cost effective$', 'cost$', economic$', 'costs and cost analysis', 'clinical adj 1 (experience$ or role$)', 'routine adj 1 (use$ or usage or applica$)' were used alone or in combination to ensure a high recall rate of the relevant references.

For each of the citations considered, the abstract was read (where available) and articles were excluded if they were outside the scope of the review. From the references identified, a selection was made and full text articles that met the following criteria were retrieved:

- articles reporting results of prospective controlled trials (randomized and non-randomized), prospective and retrospective comparative studies (with series larger than 10 subjects) in which the accuracy of each of the selected functional diagnostic imaging technologies was compared with that of the gold standard used to diagnose epilepsy
- review articles on clinical utilization, clinical indications, advantages, disadvantages, potential side effects, cost-effectiveness analysis of the selected functional diagnostic imaging technologies.

Editorials, letters, case reports and technical reports were excluded unless they provided pertinent information on the characteristics of the assessed techniques, their cost, advantages and limitations, that was available elsewhere.

Further relevant articles were found by examination of the reference listed in the retrieved papers. Reports published before 1993 were quoted when appropriate.

The methodological quality of the primary studies located in the literature search was considered in terms of the criteria formulated in Appendix B. These criteria were formulated having regard to the information needed to confidently evaluate the use of the selected functional diagnostic imaging technologies in terms of diagnostic accuracy and clinical validity, in order to define their place in routine diagnostic use.

# Appendix B: Quality of studies

In assessing the usefulness of the studies of FDI in epilepsy, there seems a need to consider both the scope of the trials and their methodological quality. The scope relates to the type of classification put forward by Fineberg et al. (31) and various other groups and might include:

- *Technical performance.* Was the FDI method known or shown to be capable of producing acceptable image quality and achieving other performance criteria?
- *Diagnostic accuracy.* Was the accuracy of the diagnosis/information from the FDI method compared with information from alternative diagnostic methods for the condition, or other sources of data?
- *Effect on the management decision.* Did the use of FDI influence the decision on whether to perform the reference method (invasive EEG)? Did information from the FDI exam contribute to decisions by physicians on future management of patients?
- *Effect on health outcomes.* Did protocols which included use of the FDI method affect patient outcomes differently than other approaches?

Not all studies of diagnostic technologies will include each of these dimensions, but in each case there is a need to consider methodological quality of the evaluation undertaken. Design of the study, inclusion of all relevant information and analysis of data are important considerations. In practice, reports on FDI and other diagnostic information frequently include only limited information on a number of areas. Nevertheless, consideration of the following points is required:

*Study design:* prospective/retrospective; controlled/not controlled; randomized or not.

*Description of study population:* subjects and controls were adequately described (number; sex; age; source of recruitment; consecutive/not consecutive; type, severity, history of disease). Inclusion and exclusion criteria adequately described.

*Characteristics of the assessed diagnostic method:* technical factors (relating to performance of the FDI method and interpretation of its findings) that can be source of bias were adequately described. (Objective criteria for presence or absence of disease as defined by the assessed method; type of equipment; method of performing the test; reproducibility of results obtained by the assessed method; variation in interpretation between observers).

*Determination of diagnostic accuracy and validity:* the assessed method was independently compared with a reference method; blind comparison was used and adequacy of blindness was assessed; statistics on analytical performance were reported; all subjects were evaluated by both the reference method and the assessed method; confidence intervals were reported; assessment of whether the FDI findings influenced the decision to perform the reference method.

*Influence on management:* the role of the assessed FDI method was determined (e.g., additive or replacement method); there was determination of whether decisions about treatment and other management options can be based on data from the assessed method.

*Influence on outcomes:* follow-up of treated and untreated subjects, including those in whom the assessed method did not provide diagnostic information; clear specification of clinically relevant outcome measures.

# Appendix C: Description of FDI technologies

The following notes provide brief additional details of FDI technologies.

### *Positron emission tomography*

PET is a versatile FDI tool capable of providing dynamic information regarding the biochemistry and physiology of the brain. It tracks the activity of a radio-isotope injected into the body. The radio-isotope emits a small positively charged particle (a positron) on decay that travels only few millimeters within tissue before colliding with an electron. The collision releases energy in the form of 2 gamma rays or annihilation photons. When the gamma rays (which exit at 180 degrees to each other) strike paired, oppositely placed, detectors simultaneously, they register as a coincident event. The information for image reconstruction is accumulated from these coincidences. Several paired detectors are placed circumferentially to capture a large number of coincident events.

Computer tomography reconstruction algorithms are used to generate a three dimensional image from a series of radiation measurements (which represents the spatial distribution of the tracer). A mathematical model is used to convert the PET scan image into quantitative information. The model uses assumptions and metabolic models about the biochemical properties of the administered radio-pharmaceutical, the compound that incorporates the radio-isotope. In most PET applications, the radio-pharmaceutical and is biologically active in the body. Information provided by PET may be overlaid or imprinted onto MRI for improved anatomical localization of the detected activity.

PET is a nuclear medicine method that utilizes radio-pharmaceuticals with relatively short half-lives (minutes to hours). The type of information obtained with PET depends mostly on the radio-pharmaceutical used. Research and clinical work utilize radio-isotopes of carbon, oxygen, nitrogen and fluorine. Clinically useful paradigms include the measurement of cerebral blood flow, blood oxygenation, receptor binding and glucose metabolic rates.

### *MRS/MRSI*

MRS has been developed as a direct medical application of nuclear magnetic resonance spctroscopy which has been used in chemistry and biochemistry for many years. It can determine, non-invasively, the presence and relative quantities of various compounds in tissue using an MRI system. (20;21;81)

MRS exploits the principle that, when placed in a magnetic field, chemically distinct nuclei in a compound resonate at a slightly different frequency. The resonance depends on the strength of the applied magnetic field and on the local magnetic environment in the molecule created by the surrounding electron cloud. In a group of resonating nuclei, small differences in resonance frequencies (called chemical shifts) can be detected depending on the position of the nuclei in a specific molecule. This information is usually displayed in the form of a graph or spectrum in which signal intensity is plotted against frequency and in which area under the trace indicates the signal amplitude at that frequency. Peaks corresponding to specific molecules can be differentiated and the quantity of particular chemical components can be estimated by measuring the area under the spectral peak for each compound. (20;26;59)

Non-invasive in vivo MRS studies in humans have been carried out with nuclei that have high natural abundance and are present in large amounts in biologic structures of clinical importance. The most commonly used spectra are those of hydrogen (1H) and phosphorus (31P). (20;26;59)

In general, MRS is considered to be a safe diagnostic procedure. However, hazard from ferromagnet implants (e.g. clips, protheses, pacemakers) is increased at magnetic fields hight than 1.5 Tesla and it has been recommented that MRS examination is avoided during the first trimester of pregnancy. (20)

Close attention to quality control of all apsects of MRS methods has been recommended. The potential risk of introducing artifacts and errors is high at many points in the procedure and they may not be detected. Recently, the European Community has developed at protocol for quality control of MRS studies. (10;20)

MRSI studies are comre complex than MRI studies (requiring additional software and somethimes hardware) and they have been performed by physicists, biochemists and physicians with specific training rather than by technologists. (10;20) Time and space resolution remain major limiting factors for MRS. The resolution of the voxels (spatial resolution ) is limited by the desired signal-to-noise ratio, the tissue concentration of the metabolites of interest and the amount of available scan time (a patient cannot be kept in the MRI system long enough to perform all the different measurements). (81) A standard MRS takes from 30 minutes to 2 hours. (20;26)

### *Functional MRI*

Functional MRI defines a class of non-invasive or minimally invasive MRI-based techniques. In these, the use of special scanning sequences and, in some cases, the utilization of contrast media, sensitizes image acquisition to the local metabolic and hemodynamic changes that occur when the brain is activated or stimulated by various tasks or by cognitive processes.

Based on the assumption that neuronal activation is closely coupled with local hemodynamic and metabolic changes, functional MRI evaluations use difference images of the stimulated and non-stimulated brain to visualize MRI signal differences between two acquisitions obtained during different neurologically active conditions. The analysis approach commonly used compares baseline or non-stimulated states with activity during the performance of sensory or cognitive tasks. For example, sensory stimuli are processed,

motor functions are performed, sensory experiences or motor activities are imaged, and cognitive tasks are executed. Alternatively, a comparison may also be made between two tasks where it is reasonably certain that the loci of activation do not overlap. (83) The resulting image provides an anatomical image of the brain as well as the functional location of cortical activity associated with the stimulated state.

Initial functional MRI studies of the activated brain used bolus injections of paramagnetic contrast agents, usually of gadolinium diethyenetriamine penta-acetic acid (Gd-DTPA). These studies measured changes related to cerebral blood volume and/or cerebral blood flow based on signal changes following contrast agent injections. A drawback of this technique is that the bolus of contrast agent must be injected for each task and repetitive studies on a single subject are precluded.

Functional MRI also permits visualization of activated brain regions in a non-invasive fashion (without injection of contrast agents). The most common non-invasive approach for brain activation studies, the "blood oxygen level dependent" (BOLD) technique, uses blood as an endogenous contrast agent and detects changes in blood oxygenation corresponding to changes in regional cerebral blood volume and flow. Image intensity can become darker if there is more deoxygenated blood and brighter if more oxygenated blood enters the brain. Another non-invasive functional MRI technique, the in-flow method, is available but has been less used than BOLD technique.

The BOLD method provides an indirect measure of local brain activation. The technique has been reported to detect changes in local oxygenation (oxyhemoglobin to deoxyhemoglobin ratio) caused by metabolic (oxygen utilization) and hemodynamic (tissue perfusion) responses to a perturbation. Blood oxygenation changes can be imaged continuously while functional centres are being stimulated. (1;75) However, these responses represent a relatively indirect correlate of the neuronal activity, and it is yet unclear how the observed changes are related to the neuronal activity of interest. (6;41;81)

The BOLD method has primarily been used in scanners with high field magnets (1.5 to 4.0 T) which provide a better signal-to-noice ratio (extremely small amplitude of the signal change). (1;18;48;56;58;61;62;75;83) Specialized gradient head-only coil and radio-frequency surface coils have been produced and used to improve the signal-to-noise ratio and increase multslice echo-planar capabilities. (58)

As changes in signal intensity related to changes in blood flow during brain activation are very small, measurements depend use of on algorithms which make it possible to distinguish between the signal associated with the mental task and the resting or control pattern. Different methods have been used in centres studying functional MRI. Simple subtraction between activated and baseline images can be used but remains sensitive to motion artifacts. Other approaches, such as correlation analysis, principal component, and Fourier analysis have been used to semiquantitate signal changes. Also, various processing strategies, such as gradient recalled (GRE) images, echo-planar imaging (EPI), and other fast scanning techniques have been developed and used to acquire or generate BOLD functional MRI signals on scanners with different field strengths. (1;56;58;61;75;83)

According to the reviewed literature, with the BOLD method there is sensitivity not only to local blood oxygen level but also to in-flow effects, large vessels and motion artifacts. There is concern that all these may produce errors in localizing the centre of the functional blood flow response. (1;6;18;41;48;56;61;62;75;105) EPI has been advocated in order to overcome some of these problems. (1;62) However, this technique is expensive and not widely available. Although it may be much faster than conventional imaging, its spatial resolution is worse. (6) Also, interimage motion artifacts are a serious problem for functional MRI using EPI. (56;62)

Various approaches have been taken to minimize motion artifacts. Physical restraints including such devices as bite bars, face masks and vacuum-pack head molds have been developed and used to reduce head motion artifacts. (18;62) Difference noise reduction algorithms are being developed to reduce signal fluctuations from physiologic processes such as cardiac pulsations, respiration and cerebral pulsation that may be incorrectly interpreted as functional activation. (58;62)

As with other MR methods, patients with pacemakers and magnetic implants must be excluded. (61)

As information concerning potential confounding factors (e.g. effects of large vessels and stimulus-correlated motion) is acquired with functional MRI, there have been speculations that similar difficulties may apply to PET. (1)

The hemodynamic response time (the physiological time course of the cerebral blook flow change following functional activation) limits the temporal resolution of functional MRI. (1;48)

### *MEG/MSI*

MEG is a complex non-invasive technique that measures extremely weak neuro-magnetic fields (about one-billionth the strength of the earth's magnetic field) outside the head by means of super-conducting sensors. Super-conducting gradiometer coils detect the magnetic fields and their induced signals are then amplified by super-conducting quantum interference devices (SQUIDs). These detectors are maintained in an superconducting state by immersion in liquid helium contained in a thermally insulated cryogenic container.

MEG technique attempts to detect, measure, record and analyze the extra-cranial magnetic fields induced by the electrical activity of the brain. The basic idea is to identify the intra-cranial currents by measuring their induced magnetic fields outside the head and to thereby localize areas of neuronal activity in their temporal development.

The raw data are filtered and subjected to mathematical modeling to estimate the location, strength and orientation of the current sources in the brain associated with the magnetic fields. (93) Initial recordings superficially resemble the EEG findings. Further processing gives a topographical map of the brain showing the distribution and time evolution of the located current sources.

MEG systems have evolved from single channel instruments to large arrays instruments offering full-head coverage with 64 to 150 channels. The technologyuses sophisticated operating and data processing equipment and it is usually combined with MRI to portray the spatial distribution of the sources of the measured magnetic fields relative to anatomy (this combined approach is called magnetic source imaging or MSI).

Sources of MEG source localization error include probe prosition errors, environmental and instrument noise and mathematical modeling errors. (37;67;87) The reported localization error is less than 1 cm. (6;67)

Magnetic or electrical objects such as some dental work, steel surgical clips, pacemakers or other implants may introduce magnetic artifacts sufficient to interfere with the MEG. (28;37;67;86)

The limitations of this method include its high cost, the requirement of the magnetically shielded room and slowness of data acquisition. (5;87;103;107) The MEG examination time varies according to the sensor array size (number of channels) and type of mapping paradigm. (67;87) Although recording time has improved with the new multichannel whole-head systems (122-channel or more), the typical MEG examination is complex and requires about 1-2 hours. (5;87)

The MEG method of current source localization is based on the solution of the inverse problem. That is how to determine internal sources on the basis of measurements performed outside the head. Since there are many potential combinations of sources which could produce any observed magnetic field pattern some assumptions must be made about the source. Calculation of the dipole (the signal generator) locations requires several physiological constraints or additional information. (6;28;37;38;43;64;81;86) The active brain areas, generating the signal, are modeled as current dipoles, which are assumed to be situated in a sphere of homogenous activity.

The most commonly used model is the single equivalent current dipole (SECD). However, it is generally accepted that SECD is a crude approximation of the underlying activity. (28;37;49;51;86) In many cases the MEG data cannot be accurately explained by a single current source (the larger the source the more the SECD may depart from the physical reality, increasing the possibility of error; it does not account for multiple active neuronal sources.) (37;42;49;76;85) More general approaches including multiple current dipole models and distributed current souce models have been proposed as alternatives to SECD. (37;49;64;85;86;93)

MEG is preferentially sensitive to superficial electrical currents tangential to the skull. This makes the computational analysis simpler but makes MEG "blind" to deep and radial current sources. (15;37;42;51;64;70;71;87;89;90;96) Therefore the exact location of the current sources requires additional information from another brain imaging technique. (76;96)

# Appendix D: Studies of FDI methods in management of epilepsy

## Table Abbreviations

| | |
|---|---|
| 1HMRS/ MRSI | proton MRS/MRSI |
| MRI | magnetic resonance spectroscopy |
| AM | amygdala |
| AMT | anteromesial temporal |
| AI | Asymmetry index |
| BTE | bitemporal epilepsy |
| Cho | choline |
| CI | confidence interval |
| CPS | complex partial seizures |
| Cr | creatine |
| ECD | equivalent current dipole |
| ECoG | electrocorticography |
| EEG | electroencephalography |
| ETLE | extra temporal lobe epilepsy |
| EZ | epileptogenic zone |
| F | females |
| Fmri | functional MRI |
| HA | hippocampal atrophy |
| HF | hippocampal formation |
| HS | hippocampal sclerosis |
| IEEG | invasive EEG |
| M | males |
| MEG | magnetoencephalography |
| MI-CPS | medically intractable complex partial seizure(s) |
| MRE | medically refractory epilepsy |
| MRI | magnetic resonance imaging |
| MRIV | MRI volumetry |
| MRS | magnetic resonance spectroscopy |
| MRSI | magnetic resonance spectroscopy imaging |
| MRTLE | medically refractory temporal lobe epilepsy |
| MSI | magnetic source imaging |
| MTS | mesial temporal sclerosis |
| NAA | N-acetyl-aspartate |
| NSS | not statistically significant |
| PET | positron emission tomography |
| PPV | positive predictive value |
| pt(s) | patient(s) |
| rCGR | regional cerebral glucose rate |
| rCMRglu | regional cerebral metabolic rate for glucose |
| rCP | regional cerebral perfusion |
| RF | radio frequency(ies) |
| ROI | region of interest |
| Se | sensitivity |
| SEEG | stereo EEG |
| Sp | specificity |
| SPECT | single photon emission computed tomography |
| SS | statistically significant |
| TH | temporal hypometabolism |
| TL | temporal lobe |
| TLE | temporal lobe epilepsy |
| VEEG | video- electroencephalography |
| VOI | volume of interest |
| XTM | extra mesial |
| y | year(s) |

# Table 3: Studies on the use of PET for epilepsy

| Study | Patients | Method | Diagnostic accuracy | Conclusions | Comments |
|---|---|---|---|---|---|
| (7)<br>Benbadis et al., 1995<br>Retrospective study<br>(Jan. 1, 1990-Dec. 12, 1992) | *n=25 MRTLE pts (interictal/ ictal BTE on surface EEG; 12M/13F; 19-50y; no MRI mass lesion)<br>*neurologic history, physical examination, surface EEG +video monitoring, MRI, neurophysiologic testing, intracarotid amobarbital test (for language and memory); *15/25 (60%) had invasive evaluation and surgery; 14/15 had 1y follow-up | *FDG PET (Posicam; 5.8 mm FWHM) before invasive EEG; continuous EEG before and during PET;<br>*PET scans visually analyzed by 3 observers blinded to depth EEG | *PET: in 10/25 pts (40%) did not lateralize (no significant asymmetry); 9/10 pts had bilateral hypometabolism; PET 's lateralization (vs. depth EEG): Se of 67% (10/15pts ); Sp of 60%; PPV of 91%; in 10/25 pts (40%), PET concordant with MRI;<br>*PET did not lateralized in 23/25 pts (9/23 true negatives; 6.7% Se; 90% Sp) when 20% hypometabolism criterion was used<br>*PET agreed with depth EEG in 9/14 pts with surgery; 6/9 pts seizure free; 1/9pt with rare seizures (combined surgical success, 78%) | *convergent ictal depth EEG, PET and MRI do not guarantee surgical success; however, in light of 100% lateralization by depth EEG, nonlateralized PET and MRI don't indicate poor surgical outcome<br>*data suggest that surgical success rate is almost identical in pts with convergent depth EEG and PET data compared with that in pts selected by depth EEG alone (7/14 vs. 8/14)<br>*in this highly selected group of patients, the laterilizing value of PET and MRI was somewhat diminished | *inadequate description of pt population<br>*no randomization, no controls for PET<br>*tests not adequately described<br>*reproducibility not assessed<br>*variation in interpretation not evaluated<br>*adequacy of blindness not evaluated<br>*not determined whether PET influence decision to perform reference standard (more than one)<br>*PET used to confirm localization and lateralization<br>*no information on CI |
| (13)<br>Chee et al., 1993<br>Retrospective study<br>(Feb 1989-Oct 1990) | *n=40 MRTLE pts (based on clinical symptoms and interictal EEG, with no structural lesion on MRI; 25M/15 F; 18-53 y; epilepsy duration: 3 to 36y); only focal/regional ictal onset were considered in lateralizing seizure focus<br>*38/40 had surgery with at least 1 y follow-up | *FDG PET(Posicam; 5.8 mm FWHM); 9 pts visually analyzed (no knowledge of EEG); 31 pts analyzed semiquantitatively (continuous EEG monitoring before and during FDG uptake)<br>*unilateral interictal temporal spikes (ITS) recorded using scalp EEG | *ITS in 33/40 pts (82.5%); 89.2% Se;100% PPV, as compared to invasive EEG in 37 pts<br>*PET hypometabolism in 33/40; Se of PET alone (detecting epileptogenic zone in TLE pts with unilateral ictal focus) was 78.4% (31/37 identified by invasive EEG) and PPV of 93.5% (29/31); unilateral TH in 31/40 (77.5%); in 29/31, side showing TH in agreement with final EEG localization<br>*28/40 pts (70%) had concordant unilateral TH and ITS; Se of 75.7%; PPV of 100%<br>*no SS difference (Fischer's Exact Test, p=0.54) in 1y surgical outcome noted between pts with unilateral TH and those without | *unilateral ITS predict a good outcome following temporal lobectomy in TLE pts with no mass lesion on MRi<br>*there is a high correlation between PET local hypometabolism and epileptogenic region identified by depth-electrode verified ictal onsets<br>*use of PET provides corroborative lateralizing information but PET that fails to show unilateral TH does not preclude a good surgical outcome | *no randomization, no controls<br>*reproducibility not measured<br>*PET used lateralize the abnormal TL<br>*adequacy of blindness not evaluated<br>*variation in interpretation not evaluated<br>*not determined whether PET influence decision to perform reference standard (more than one)<br>*no information on CI |
| (17)<br>Chugani et al., 1993<br>Presumed prospective study (not clear from the paper)<br>(Nov 1987-Sep. 1992) | n=23 infant spasms pts (5months-3 y; 13F/10M; no remote infant spasms history; undergoing surgery; follow-up: 4-67 months)<br>*continuous EEG/video-EEG (all); MRI (all), CT (most); evoked potentials (all); sodium thiopental activation (some cases); intraoperative ECoG (*# of pts not mentioned)* | *FDG/PET (NeuroCAT or CTI 831)<br>*presurgical evaluation depended on visual analysis of patterns of cerebral glucose metabolism (by one of the authors); oral chloral hydrate sedation | * CT/MRI structural abnormalities in 7/23<br>*PET: 18/23 had focal hypometabolism; 5/23 had diffuse hypometabolism; in 14, PET demonstrated cortical abnormality in absence of obvious CT/MRI abnormality; pts with normal CT/MRI and PET scans had no surgery (convergence of EEG and imaging data a prerequisite to surgery)<br>*good correspondence between EEG and PET localization<br>*1pt with PET defined foci is seizure free after 62 months; other 6 are doing 'reasonably well, but continue to exhibit some degree of developmental delay | *" the postsurgical outcome can be quite good in some children with infantile spasms, particularly when the epileptogenic area is visualized only by PET"<br>*"longer follow up will be required to evaluate the full impact of surgical intervention in these children"<br>*"Occasionally, the degree of focal cortical hypometabolism on PET can be quite subtle. This is particularly problematic in infants younger than 1 year of age..." | *inadequate description of pt population<br>*no randomization, no controls<br>*tests not adequately described<br>*reproducibility not assessed<br>*no information on who interpreted findings and on blindness<br>*not determined whether PET influences decision to perform reference standard (more than one)<br>*PET used to confirm localization/lateralization<br>*no information on CI |

## Table 3: Studies on the use of PET for epilepsy (continued)

| Study | Patients | Method | Diagnostic accuracy | Conclusions | Comments |
|---|---|---|---|---|---|
| (46)<br>Helveston et al., 1996<br>Presumed prospective study (not clear from the paper) | *n=16 consecutive MRTLE pts (10M/6F; 14-45y; no obvious structural lesions); all had epileptic drugs; all had surgery (lateralization and localization proved by Engel's class I/II at 1 y follow-up);<br>*convergent data from scalp/sphenoidal (all) and invasive EEG (11/16 pts) Wada test, qualitative MRI (only), interictal SPECT, neuropsychological tests, qualitative PET | *interictal+ictal EEG reviewed by at least 2 certified encephalographers<br>*PET (ECAT 951; 6-8 mm FWHMM); scalp EEG before and during PET; scans interpreted prospectively by 1 investigator (blinded to all pertinent clinical data) by visual analysis<br>*MRI (1.0T) interpreted prospectively by 1 investigator (blinded to all relevant clinical data); hippocampal volumes measured (volumetric MRI) by an examiner (blinded to pts' names, clinical and other data) | *PET correctly lateralizing in 9/16 (56%); nonlateralizing in 6/16 (37.5%); incorrectly lateralizing in 1/16 (6%)<br>*qualitative MRI lateralizing in 6/16 (37.5%); nonlateralizing in 6/16 (37.5%); incorrectly laterilizing in 4/16 (25%)<br>*quantitative/volumetric MRI correctly lateralizing in 16/16 (100%)<br>*age at onset, seizure duration, and total number of seizures did not correlate with PET, qualitative MRI and volumetric MRI lateralization<br>*all became seizure free or had rare seizures | *each technique yields useful information for seizure lateralization in TLE pts considered for surgery<br>*volumetric MRI yields considerably more information than PET and qualitative MRI for seizure lateralization in TLE pts considered for surgery | *no randomization, no controls<br>*reproducibility not assessed<br>*variation in interpretation not evaluated<br>*adequacy of blindness not evaluated<br>*not determined whether PET influence decision to perform reference standard (more than one)<br>*role of PET was to confirm localization and lateralization<br>*no information on CI<br>*test not sufficiently described |
| (66)<br>Lucignani et al., 1996<br>Double-blind prospective study | *$n_1$=16 MRE pts (all under drug treatment; 19-42y; 8M/8F; all had physical+neurological exam, standard interictal+ictal scalp EEG, VEEG, MRI)<br>*$n_2$=17 healthy controls (18-69y, not receiving drugs, no history of seizures) | *[$^{18}$F]FDGPET (ECAT 931/04-12, Siemens/CPS, 8.5 mm FWHM) under scalp EEG monitoring, at least 24h after last seizure; visually analyzed by 3 physicians blinded to epilepsy type<br>*quantitative PET using rCMRglu<br>*1.5 T MRI unit<br>*SEEG after PET (gen. anesthesia), interpreted by nuclear medicine physicians unaware of SEEG features by neurologists unaware of PET results | *visual analysis: temporal hypometabolism in all pts (in additional areas in a few cases)<br>*quantitative assessment of rCMRglu : abnormal metabolic rates in 38% of areas with abnormal SEEG and in 23% of areas with normal SEEG;<br>*poor agreement between SEEG and FDG-PET (K=0.107) | *FDGPET allows rapid whole brain examination, with limited temporal and spatial resolution<br>*FDG PET quantitative data in MRE pts is neither a specific nor a sensitive feature of any of different SEEG patterns<br>*FDG-PET data might be useful as a complement to morphological, clinical and SEEG data<br>*PET's intrinsic value still needs to be determined in relation to surgery outcome | *eligibility criteria not clearly described<br>*no randomization, small sample size<br>*reproducibility not assessed<br>*variation in interpretation between observers not evaluated<br>*abnormality not clearly defined<br>* tests not described sufficiently<br>*PET used to confirm localization<br>*accuracy statistics not reported<br>*not clear who analyzed quantitative PET<br>*adequacy of blindness not assessed<br>*not determine whether PET influenced decision to perform reference method |

## Table 3: Studies on the use of PET for epilepsy (continued)

| Study | Patients | Method | Diagnostic accuracy | Conclusions | Comments |
|---|---|---|---|---|---|
| (69)<br>Mastin et al., 1996<br>Prospective study<br>(July 1991-Oct. 1993) | *n=35 MRE pts (25M/10F; 13-45y; 6/35 ETLE, 29/35 TLE; all had antiepileptic drugs, EEG and MRI; all had surgery with up to1 y follow-up; clinical outcome data according to Engel's classification);<br>*all had interictal (n=33) or postictal SPECT (n=23); 25 pts had FDG PET; 20 pts had invasive EEG | *FDGPET (ECAT 951, 5-7 mm FWHM) (EEG monitoring before and after FDG injection);<br>*PET and SPECT (triple headed camera, Triad, Trionix Research Laboratory, 6-8 mm FWHM) blindly and retrospectively reviewed by 3 radiologists (1 for PET, 2 for SPECT, blinded to pt data, surgical site, results of other tests) who interpreted them prospectively too (blinded to clinical data, results of functional imaging and non-imaging tests; qualitative MRI data available)<br>*prospective and retrospective PET and SPECT compared in pts and correlated with site of surgery | <u>PET vs interictal SPECTvs. Posticta SPECT (in all pts):</u><br>*Se: 60% vs. 61% vs. 52%; correct localization: 15/25 vs. 20/35 vs 12/23; (p=0.999); incorrect localization: 3/25 vs. 8/33 vs. 10/23; (p=0.625); PPV (all sites): 83% vs. 71% vs. 55%; PPV (temporal sites) 94% vs 83% vs. 53%; PPV (extratemporal sites): 33% vs. 20% vs. 50%<br><u>PET vs interictal SPECT vs. posticta SPECT in pts with no MRI mass lesion:</u><br>*Se: 57% vs. 72% vs. 42%;PPVs (all sites): 81% vs. 78% vs.44%; PPV (temporal sites):93% vs. 81% vs. 50%; PPV (extratemporal sites): 0% vs. 50% vs. 50%<br>Agreement between prospective and retrospective data was good for PET and posticta SPECT and excellent for interictal SPECT;<br>PET and SPECT had SS reproducibility when interpreted by subspecialty readers: p=0.004 (PET); p<0.001 (SPECT, reader 1 and 2)<br>*all 15 pts with correct localization by PET had no seizures or rare seizures after surgery<br>*18/20 pts with correct localization by interictal SPECT had successful clinical outcome (2 had worthwhile improvement) | *PET and interictal SPECT have statistically similar seizure focus localization capabilities when directly compared in individual pts; PET'PPV is greater in all pts but comparable to that of interictal SPECT in pts with no MRI mass lesions<br>**interictal SPECT is an alternative to PET in these pts.( higher false-localization rates must be taken into consideration)<br>*role of functional imaging in the evaluation of pts with epilepsy may be to clarify ambiguous MRI results | *not adequate description of pt<br>*no randomization, no controls<br>*eligibility criteria not clearly defined<br>*imaging tests not perform all on same pts; reasons not clear<br>*not clear who did prospective interpretation of PET<br>*no information on CI<br>*PET used to confirm localization<br>*abnormality not clearly defined<br>*tests not described sufficiently<br>*adequacy of blindness not evaluated<br>*not determined whether PET influenced decision to perform reference method |

## Table 3: Studies on the use of PET for epilepsy (continued)

| Study | Patients | Method | Diagnostic accuracy | Conclusions | Comments |
|---|---|---|---|---|---|
| (68)<br>Markand et al., 1997<br>Retrospective study | *n=67 MI-CPS pts (had surgery; 38F/29M;10-55.5y)<br>*all pts had usual antiepileptic medication<br>*all had completed video EEG monitoring before PET<br>*seizures localized by combined data from MRI, interictal and ictal EEG, neuropsychometric tests, thiopental activation test, intracarotid sodium amytal test, interictal and ictal SPECT, interictal PET | *interictal FDG PET (Siemens ECAT; CTI 951/31R; 6.5 mm FWHM) in 55/67; EEG during PET study<br>*interictal (HMPAO)and ictal (ECD or HMPAO) SPECT (Elscint Helix dual headed rotating gamma camera; 30-40min); interictal SPECT in 53/67 pts and ictal SPECT in 44/67pts<br>*SPECT and PET interpreted visually by 1 or more well experienced nuclear medicine physicians (blinded to EEG and other localization data) and by neurologists;<br>* MRI in 66/67 pts, many had volumetric analysis | *interictal SPECT: 69.8% Se (decreased rCP); 88.1% (37/42pts) PPV for localization (asymmetric rCP in 42/53 pts)<br>*ictal SPECT; 70.5% Se (ictal hyperperfusion); 96.9% PPV (31 had increased rCP corresponding to TL and 32 had ictal hyperperfusion ); 86.4% Se and 97.4% PPV of ictal scan in demonstrating either hyper- or hypo-perfusion<br>*PET: Se (hypometabolism): 80% (44/55) to 85.5% (47/55); 100% PPV; in most pts, diffuse hypometabolic area involving mesial and lateral temporal structures<br>*both ictal SPECT and interictal PET in 36/67 pts (either normal MRI or evidence of MTS); PET definitive in 30/36 and questionable in 2 pts (useful localization in 32/36); ictal SPECT correct in 27/36 (ictal hyperperfusion); probable in 7/36 (ictal hypoperfusion) (useful localization in 34/36); NSS difference between their Se values (in 6/36 pts they were complementary to each other in providing localizing data)<br>*unilateral mesial temporal lesion on MRI in 43/66 pts, (65.2 % Se); 22/23 MRI negative pts had both SPECT and PET; both provided localization in 16/22 pts | *in 23 MRI negative pts both interictal PET and ictal SPECT played critical roles in the decision to recommend surgical resection without additional invasive electrographic monitoring; in 6/23 they were complementary to each other ;<br>*the most rational strategy in pts with MI-CPS undergoing presurgical evaluation would be to obtain ictal SPECT and interictal PET in pts with difficult or unclear localization on their scalp EEG and MRI studies, which would reduce the invasive EEG monitoring to the minimum | *inadequate description of pt population<br>*no randomization, no controls<br>*tests not adequately described<br>*reproducibility not assessed<br>*variation in interpretation not evaluated<br>*adequacy of blindness not evaluated<br>*role of PET was to confirm localization (plan management)<br>*no information on CI |
| (84)<br>Radke et al., 1994<br>Presumed prospective study (not clear from the study) (14 months) | *n=54 consecutive MRE pts (6-45y; 35 TLE pts and 19 ETLE pts); all had at least one antiepileptic drug; post-surgical follow-up:24-40 months<br>*prolonged EEG/close circuit TV telemetry; extensive interictal EEG recordings, MRI and neurophysiological tests in all; invasive EEG in 13 pts (no MRI abnormalities) | *MRI (GE Signa 1.5T), read by 2 radiologists blinded to PET and EEG<br>*PET (ECAT III; CTI; FWHM=8.6 mm) and randomly visually interpreted by 2 blinded observers (*not mentioned what they were blinded to and method of randomization)*; in pts with frequent clinical or subclinical EEG seizures (*not mentioned how many)* EEG monitoring first 20-30 min. of FDG uptake phase | *27/35 TLE pts (77%) had unilateral hypometabolism that correlated with EEG<br>* PET abnormalities in ipsilateral temporal lobe in 12/35 TLE pts (34%) with focal MRI abnormalities;<br>*6/19 ETLE pts (32%) had abnormal PET;<br>*7/19 ETLE pts had MRI abnormalities; 2/7 had diffuse hemispheric PET abnormalities; 5/7 had normal PET<br>* 4/13 pts with invasive EEG had TLE;3/4 (75%) had PET abnormalities; 9/13 had ETLE; 2/9 (22%) had PET abnormalities<br>*30/35 TLE pts had follow-up data after surgery ; 6/19 ETLE had surgery; | *MRI appears superior in identifying epileptogenic lesions in ETLE pts<br>"PET is of less clinical utility in the presurgical evaluation of pts with extratemporal epilepsy as compared to pts with temporal lobe epilepsy" | *incomplete description of pts<br>*variation in interpretation between observers not evaluated<br>*reproducibility not assessed<br>*no randomization, no controls<br>*tests not adequately described<br>*PET abnormality not clearly defined<br>*adequacy of blindness not assessed<br>*PET used to confirm localization<br>*no information on CI<br>*not determined whether PET influenced decision to perform reference method |

## Table 3: Studies on the use of PET for epilepsy (continued)

| Study | Patients | Method | Diagnostic accuracy | Conclusions | Comments |
|---|---|---|---|---|---|
| (102)<br>Theodore et al., 1997<br>Prospective study | *n=46 pts with MI-CPS (no MRI mass lesion, surface ictal EEG not localizing)<br>*all had invasive EEG<br>*35/46 had surgery based on invasive EEG (follow-up: 12-113months); based on data from prolonged ictal VEEG and MRI, decision to place subdural/depth electrodes made by investigators blinded to PET | *PET (NeuroPET, Scandronix 1and 2; similar resolution); standard template for image analysis and quantitation of regional metabolic rates; using template, an AI (cutoff of 0.15) was calculated for lateral temporal, mesial temporal, parietal, inferior frontal and superior frontal regions<br>*formal volumetric MRI measurements were not made uniformly | *26/46 pts had TL hypometabolism; 25/26 pts had ipsilateral seizure onset on IEEG; 23/25 had surgery; 18/23 were seizure free<br>*5/46 had unilateral frontotemporal hypometabolism and TL IEEG seizure onset; all had surgery; 3/5 were seizure free<br>*1/46 had frontal/not temporal hypometabolism; did not have surgery (frontal and temporal IEEG seizure onset)<br>*14/46 had no PET lateralization; 7/14 had surgery; 4/7 were seizure free<br>*no pt had discordant PET and MRI lateralization | *pts with positive MRI more likely to have FDG/PET lateralization and tended to have localization on IEEG studies<br>*FDG/PET more sensitive than MRI in lateralizing EZ (*however*, "some pts may not have had optimal MRI studies and pts with obvious MRI abnormalities may have been less likely to be referred to us")<br>*"Hospital admission for drug discontinuation and ictal VEEG monitoring may be unnecessary and may even provide misleading information when FDG-PET as well as other imaging tests such as MRI show localization consistent with interictal EEG and clinical evidence. Using this approach, number of pts who require IEEG can be reduced significantly" | *inadequate description of pts<br>*no randomization, no controls<br>*insufficient information on type of PET equipment<br>*test not adequately described<br>*reproducibility not determined<br>*variation in interpretation not evaluated<br>*adequacy of blindness not evaluated<br>*not clearly determined whether PET influenced decision to perform reference standard<br>*role of PET was to confirm localization<br>*no information on CI |
| (104)<br>Valk et al., 1993<br>Prospective study<br>(1 year) | *n=11 MRE pts (probable MTS, no structural lesion on MRI);<br>*non-invasive interictal/ictal EEG with video telemetry; invasive EEG (2 pts), neuropsychologic test, MRI<br>*follow-up of 2-4 years after surgery | *FDG PET (PET 600; 2.6 mm FWHM) limited to TL; assessed independently by 2 observers blinded to clinical, telemetric and imaging data (one during the study and the other one at a later time) | *10/11 had TH (91%); 1/10 had normal PET<br>*9/11 are seizure free after surgery; 2/11 have >90% decrease in seizure frequency<br>*no incorrectly lateralizing PET results<br>*no correlation between severity of pathologic findings and degree of hypometabolism<br>*observers agreed in all cases | *"MRI and PET have complementary roles in preoperative evaluation of patients with medically refractory partial complex seizures"<br>*"The sensitivity of PET in detection of regional hypometabolism increases with instrument resolution and metabolic lesions that are limited in degree and extent may not be demonstrable with low-resolution instruments." | *incomplete description of pt population<br>*no randomization, no controls, small sample size<br>*PET used to confirm localization<br>*adequacy of blindness not evaluated<br>*tests insufficiently described<br>*not determined whether PET influence decision to perform reference standard (more than one)<br>*PET abnormality not clearly defined<br>*no information on CI |

## Table 4: Studies on the use MRS for epilepsy

| Study | Patients | Methods | Results | Conclusions | Comments |
|---|---|---|---|---|---|
| (11)<br>Cendes el al., 1995<br>Prospective study | *$n_1$=30 MRTLE pts ; detailed history and neurological examination, serial EEG (sphenoidal), intensive video-EEGtelemetry, intracranial EEG (6/30pts) | *MRI/1HMRSI (1.5T, Philips Medical Systems); average values of NAA and NAA/Cr for middle and posterior parts of TLs compared to each other and to data from 10 normal controls<br>* MRIV in all pts; inversion recovery sequence; absolute volume of AM and HF and asymmetry between sides analyzed and compared to data from 30 healthy volunteers | *1HMRSI alone and MRIV alone showed good agreement with clinical-EEG lateralization: correct lateralization in 25/30 pts (83%); *combined MRIV+1HMRSI correctly lateralized in 28/30pts, 93% (Kappa coefficient=0.88)<br>*good correlation between 1HMRSI and MRIV (Pearson correlation coefficient=0.83, p<0.0001) | *MRSI and MRIV are efficient and reliable tests for lateralization of TLE<br>*By reducing reliance on EEG, they could reduce costly prolonged hospitalization.<br>*Preliminary indications suggest that they may be useful predictors of surgical outcomes for TLE | *inadequate description of pt population<br>*no randomization, no information on controls<br>*tests not described sufficiently<br>*reproducibility not assessed<br>*study not blinded<br>*abnormality not clearly defined<br>*MRSI used to confirm lateralization<br>*not determined whether MRSI influences decision to perform reference standard |
| (12)<br>Cendes et al.,1997<br>Presumed prospective study (not clear from the paper | *n=100 consecutive MRTLE pts (45M/55F; 35.1+/-12.4y; no mass lesion on MRI; accurate diagnosis by detailed history, neurological examination, EEG)<br>*normal controls: $n_1$=21 (12M/9F; 28.2y; SD=4.5) had 1HMRSI; $n_2$=30 (17M/13F; 32.4y; SD=11.3y); $n_3$=22 (10F/12F;29.5y;SD10.2) had MRIV | *prolonged EEG (10-20 system); intracranial EEG when needed; readers unaware of MRSI and MRIV results<br>*MRI/1HMRSI (1.5T; Philips); pt's average NAA/Cr compared for each other and to data in controls; MRIV in 98/100 pts (2 protocols; absolute volume of AM and HF and asymmetry between sides analyzed and compared to data from controls) | *EEG: lateralization in 93%<br>*1HMRSI: abnormal in 99/100pts; bilateral in 54%; lateralization in 86%<br>*MRIV: abnormal in 86/98 pts; bilateral in 28%; lateralization in 83%<br>*MRIV+1HMRSI: lateralization in 90% | *EEG, MRSI and MRIV were highly concordant<br>*combination of 1HMRSI and MRIV can lateralize TLE accurately and noninvasively (could reduce prolonged presurgical evaluation and make epilepsy surgery available to more pts) | *incomplete information on pts and controls<br>*inclusion/exclusion criteria not mentioned<br>*no randomization, study not blinded<br>*1HMRSI used to confirm lateralization<br>*reproducibility not assessed<br>*not determined whether MRSI influences decision to perform reference standard |
| (19)<br>Connelly et al., 1994<br>Presumed prospective study (not clear from the paper) | *$n_1$=25 MRTLE pts (10M/15F;15-45y) clinical assessment (2 independent neurologists); multiple surface interictal EEG; ictal EEG (when necessary); depth EEG (4/25pts); routine MRI (visual and quantitative T2 mapping);15/25 pts had surgery ; 14/15 followed up for more than 1 y<br>*$n_2$=13 controls (5M/8F; 19-42y; no history of significant medical illness) | *1HMRS from 2x2x2 $cm^3$ cubes, 90-180-180 spin-echo, for spatial localization; water suppression by global and local shimming<br>*corrected signal intensities from NAA, Cho and Cr and intensity ratio NAA/Cho+Cr<br>*2 criteria used to define MRS abnormalities | *NAA/Cho+cr abnormally low in 88% of pts(22/25); bilateral effects in 40%<br>*NAA/Cho+Cr correctly achieved lateralization in 15/25 pts (60%)<br>*MRS lateralization in 14/19 pts (unilateral HS on MRI and in 2 pts with no specific abnormality on MRI<br>*of 15 pts with surgery: unilateral MRS abnormalities in 8, bilateral abnormal MRS in 6, no abnormal MRS in 1 | *the findings suggest a useful role for 1HMRS in the assessment of MRTLE pts (it provides a means of identifying metabolic abnormalities within TLs, detecting bilateral pathology, and aiding lateralization of seizure origin)<br>*1HMRS can be done in a single MR examination | *incomplete information on pt population<br>*inclusion/exclusion criteria not mentioned<br>*no randomization<br>*study not blinded<br>*MRS used to confirm lateralization<br>*reproducibility not assessed<br>*not determined whether MRS influences decision to perform reference standard<br>*insufficient information on equipment used |
| (21)<br>Constantinidis et al.<br>1996<br>Presumed prospective study (not clear from the paper) | *$n_1$=20 MRTLE pts (clinically diagnosed; 11M/9F; 13-58y); MRI and combination of EEG recordings<br>*9/20 had FDG PET; 12/20 had neuropsychological exam<br>*10/20 diagnosed as resectable (clinical decision as gold standard); 9/10 had surgery<br>*$n_2$=10 volunteers had routine neurological exam and MRI/1HMRSI (used to assess NAA assymetry of TLs of non-diseased population not as controls) | *FDG PET (Siemens ECAT EXACT)<br>*MRI/1HMRSI (Philips ACSII ; 1.5T); water suppression (2 chemical shift selected RF pulses+spoiled gradient); 25 minutes for 1HMRSI; 2 criteria for visual analysis of NAA, Cho, Cr signals; lateralization by comparing visual analysis to quantitative analysis of spectra and to other data (MRI,PET, EEG, neupsychological)<br>*images evaluated by 6 reviewers (blinded to pt's name and lateralization data from other tests) | *interexaminer agreement: K=0.502 (all pts); K=0.766 (pts with NAA loss exceeding 15% in ipsilateral side) (95% CI)<br>*7/10 (70%) of resectable pts were correctly lateralized by majority of examiners<br>*3/10 (30%) of volunteers had an identifiable asymmetry in NAA by at least 4/6 reviewers | *visual examination of 1HMRSI is potentially valid in lateralizing MRTLE pts<br>*MRSI can provide an additional non-invasive tool for lateralization of MRTLE pts<br>* NAA images found to be the most effective metabolite images | *incomplete information on pt population<br>*no randomization, no information on volunteers<br>*inclusion/exclusion criteria not mentioned<br>*MRS used to confirm localization and lateralization<br>*reproducibility not assessed<br>*validity of visual analysis of 1HMRSI is assessed based on only 10/20 pts |

## Table 4: Studies on the use MRS for epilepsy (continued)

| Study | Patients | Methods | Results | Conclusions | Comments |
|---|---|---|---|---|---|
| (23)<br>Cross et al., 1995<br>Presumed prospective study (not clear from paper) | *$n_1$=20 TLE pts (14F/6M; 5-17y); clinical history, interictal and or ictal EEG to lateralize and localize seizures; sedated when necessary<br>*10/20 had surgery (clinical assessment, EEG, MRI, interictal and ictal SPECT); 2/20 awaiting surgery; 2/20 further presurgical evaluation<br>*$n_2$=13 normal adults | *MRI (1.5T Siemens, whole body); visual and quantitative<br>*1HMRS spectra from 2x2x2 $cm^3$ cubes, spatial localization by 90-180-180 spin-echo; water suppression by preirradiation of water resonance and global local shimmimg<br>*corrected signal intensity ratio NAA/Cho+Cr<br>*2 criteria to define lateralization with MRS | *abnormal MRI in 17/20 pts (unilateral HS in 15/20 pts)<br>*significant ipsilateral decreased NAA as compared to contralateral side (p=0.02) and normal data (p=0.001);<br>*Cho and Cr increased significantly bilaterally and ipsilaterally compared to normal data (p=0.03; p=0.002)<br>*NAA/Cho+Cr abnormalities in 15/20 pts (75%); 55% correctly lateralized; bilateral abnormalities in 45% | *1HMRS can contribute to the understanding of the underlying pathophysiology in TLE pts<br>*1HMRS contributes to seizure lateralization and detection of bilateral abnormalities | *incomplete information on pt population<br>*no randomization, no information on controls<br>*study not blinded<br>*inclusion/exclusion criteria not clearly defined<br>*reproducibility not assessed<br>*MRS used to confirm localization and lateralization<br>*not determined whether MRS influences decision to perform reference standard |
| (29)<br>Ende et al., 1997<br>Presumed prospective study (not clear from the paper) | *$n_1$=16 TLE pts (unilateral origin by EEG; 9M/7W; 21-49y); scalp and subdural (only when necessary) EEG;<br>*11/16 had surgery (followed up for 8-20 months)<br>*$n_2$=16 healthy subjects (11M/5W; 23-56y) had 1HMRSI too | *1HMRSI (1.5T Magnetom Vision unit, Siemens); measurement time of 13 minutes;performed with no knowledge of side of seizure focus;for quantitation: arbitrarily chosen mean metabolite relaxation times from literature for NAA, Cr, Cho, and water in gray matter were used<br>*MRI (1.5T, GE Medical Systems); images read by a neurologist blinded to seizure lateralization<br>*2 criteria used for lateralization | *9/16 pts had unilateral HA on MRI; 7/16 no MRI abnormalities; 6/7 had decreased NAA in epileptogenic hippocampus<br>*ipsilateral decrease in NAA /Cho+Cr or in NAA concentration in all pts; *decreased contralateral NAA/Cho+Cr and/or NAA concentration in 8 pts (50%)<br>*in 5/11 pts (no HA on MRI) who had surgery: outcomes correctly predicted with NAA concentration | *1HMRSI is valuable in the presurgical evaluation of epilepsy | *no randomization, incomplete information on pts and controls<br>*inclusion/exclusion criteria not clearly defined<br>*MRSI was used to confirm localization and lateralization by EEG<br>*small sample size<br>*reproducibility not measured<br>*not determined whether MRSI influenced decision to perform reference standard |
| (34)<br>Gadian et al., 1994<br>Presumed prospective study (not clear from the paper) | *$n_1$=82 MRE pts (5 y or older, children and adults; TLE in majority); combination of clinical assessment, neuropsychology, and MRI findings<br>*$n_2$=15 controls | *MRI/1HMRS (1.5T; Siemens; whole body); spectra by 2x2x2 $^{cm3\ cubes}$ using 90-180-180 spin echo; water suppression using Gaussian pulse and spoiler gradient);<br>*corrected NAA, Cho and Cr signal intensities and intensity ratio NAA/Cho+Cr | *MRE pts as a group had significant reductions in NAA signal intensity ($p<0.035$) and in NAA/Cho+Cr ($p<0.0001$), with increase in Cho ($p<0.001$) and Cr ($p<0.004$) signals as compared to controls | *1HMRS gives information that is complementary to the detailed assessment of signal intensity changes and morphological abnormalities visualized on MRI | *incomplete information on pt population<br>*no randomization, no information on controls<br>*inclusion/exclusion criteria not mentioned<br>*study not blinded<br>*reproducibility not assessed<br>*abnormality not clearly defined<br>*inadequate description of tests<br>*MRS used to confirm disease<br>*not determined whether MRS influences decision to perform reference standard |

## Table 4: Studies on the use MRS for epilepsy (continued)

| Study | Patients | Methods | Results | Conclusions | Comments |
|---|---|---|---|---|---|
| (65)<br>Lu et al., 1997<br>Presumed prospective study (not clear from the paper) | *$n_1$=12 MRTLE pts (unilateral origin; 7F/5M; 28.8+/-9.3 y); all free of observable seizures (clinical criteria), taking routine medication during PET and MRS<br>*$n_2$=26 healthy controls (14F/12M); 6/26 only MRI/MRS (4F/2M; 33.1+/-7.6y); 20/26 only quantitative FDG PET (10M/10F; 47+/-17.1y);<br>*epileptogenic TLs determined by concordant PET and EEG | *FDG PET (Scanditronix, Superpett 3000; 8mm FWHM); quantitative rCGR by metabolic index (MI)<br>*MRI/1HMRS (GE SIGNA 1.5T); PRESS to localize single voxel spectrum; CHESS for water suppression; NAA/Cho+Cr used as diagnostic index<br>*for TLE pts assymetry index (AI) to quantify relative difference between left and right TLs<br>*middle temporal cortex used to compare PET and MRS results | *5/12 pts had abnormal MRI<br>*in all pts, NAA/Cho+Cr correlated significantly with interictal glucose metabolism (r=0.54, p<0.01)<br>*mean NAA/Cho+Cr in ipsilateral side was significantly less than that in contraleteral side ((p<0.01) and less than in normal control TLs (p<0.0001)<br>*lateralization by AI of NAA/Cho+Cr consistent with EEG and PET in 5/7 pts with normal MRI | *both NAA reduction and glucose hypometabolism may originate from same underlying lesion, precise nature of which remains unknown<br>*MRS, like PET, may aid in presurgical lateralization among TLE pts without detectable hippocampal or amygdala sclerosis and atrophy | *incomplete description of pt population<br>*no randomization, small sample size, incomplete information on controls<br>*study not blinded<br>*reproducibility not measured<br>*role of MRS was to confirm PET and EEG lateralization<br>*not determined whether MRS influences decision to perform reference standard<br>*abnormality not clearly defined |
| (79)<br>Ng et al., 1994<br>Presumed prospective study (not clear from the paper) | *$n_1$=25 MRTLE pts (EEG-defined TLE, no lesion on MRI;13M/12F; 14-53y;17 unilateral; 8 bilateral);<br>*$n_2$=12 healthy volunteers | *consecutive acquisition of 1HMRSI (1.5T, Siemens) of both TLs without knowledge of pt's clinical data; data further assessed in reference to EEG results;<br>*same imaging protocol used in pts and controls | *1HMRSI: Se of 90%; Sp of 85% (as compared to EEG)<br>*difference in NAA/Cho between epileptogenic and normal TLs highly significant (p<0.001); no statistically significant difference between normal TLs and pts' uninvolved TLs | *NAA/Cho was the most sensitive and reliable quantitative marker (as compared to Cr/Cho or others) for localizing epileptogenic zone in TLE | *incomplete information on pts<br>*no information on controls<br>*no randomization, study not blinded<br>*reproducibility not measured<br>*role of MRSI was to confirm localization<br>*not determined whether MRSI influences decision to perform reference standard |

# Table 5: Studies on the use of MEG for epilepsy

| Study/design | Role of MEG/ Methodological flaws | Patients' characteristics/Techniques | Results | Conclusions |
|---|---|---|---|---|
| (2)<br>Aung et al., 1995<br><br>Presumed prospective study (not clear from the paper) | *to record bilaterally interictal activity in epileptic pts candidates for surgery<br>*resultant MSI data compared with standard MRI and EEG results<br>*study focused on characterization of interictal activity; ictal data collected also<br>* pts without detectable MRI lesions: TLE pts; TLE /ETLE pts ; and ETLE pts<br>*_no randomization, insufficient information on pt population; inclusion/ exclusion criteria not clearly defined; reproducibility not assessed; study not blind and independent;_ | *n1=30 MRE pts (13M of 6-50ys; 17F of 12-62 ys; primarily CPS, no critical health problems);<br>*n2=10 volunteers (5M of 6-46ys; 5F of 11-40ys; no history of neurological disease)<br>*dual 37-channel MEG (Magnes II, *Biomagnetic Technologies*); EEG (Neurofax, Nihon Kohden, 21-system); MRI (1.5T, Signa, GE)<br>*for typical pt. MEG took between 2-3 hr<br>*antiepileptic drugs neither withheld nor tapered<br>*epilepsy neurologist estimated location and nature of epileptic activity and implications for surgery ( medical history, MRI, EEG);he repeated analysis using MSI and compared results | *no epileptic activity in volunteers<br>*for 24/30 (80%) significant interictal activity by EEG and MSI (5 pts had no interictal/ictal activity)<br>*Lesional epilepsy:7/30 had lesions on MRI; 5/7 had interictal epileptic activity (in all MSI provided specific information on location)<br>*non-lesional cases: for 7/8 TLE pts (based on EEG), EEG consistent with MSI (added more specific and precise locations); TLE vs. ETLE: 9 pts had ambiguous EEG (TLE and ETLE); in 7/9 distinguishing information by MSI; for 2 ETLE pts (based on EEG), MSI and EEG in disagreement;<br>*in 83 % of cases, interictal MSI provided new information about location of epileptic activity | *it seems that MSI may become a cost-effective early step in epilepsy surgery evaluation<br>*validity of results must be verified by more complete studies that compare them against a gold standard (invasive EEG); if verified, present results suggest a significant potential use of MSI in epilepsy surgery program (guiding subsequent invasive EEG; modification of planned resection; indications for withdrawal for evaluation of those pts whose sources seem unsuitable for surgical correction) |
| (99)<br>Stefan et al., 1994<br><br>Presumed prospective study (not clear from the paper) | *simultaneous MEG, scalp and invasive EEG to validate the localizing capability of MEG in pts with defined unilateral TLE, with MRI lesion in the epileptogenisc lobe<br>*metric evaluation of the distance lesion and focal MEG activities<br>*_no randomization, no controls; no blinding, no adequate information on pts or selection criteria; no independent comparison; reproducibility was not assessed_ | *n=22 unilateral MRTLE pts (all had MRI abnormality)<br>* simultaneous 37-channel MEG (single ECD) scalp EEG (10/20 system) focus localizations compared with MRI-findings and postsurgical outcome<br>*focus localization and surgery performed based on non-invasive and invasive long-term video/EEG/ECoG monitoring<br>*outcome validated only in cases with>/=1 year of postoperative follow-up | * VEEG: TL epileptogenic activity in all pts (confirmed by EcoG and surgical outcome in 17 pts)<br>*in all pts MRI revealed lesions/atrophies<br>* MEG: TL epileptic activity TL in 20 pts (lobar agreement with ECoG);17/20 pts with lesions in TL had surgery (markedly improved or seizure-free); in 16/17 pts MSI showed primary focal epileptic activity localized in lobe with lesion; in tumors revealed by MRI, 73% showed a very close correlation between tumor and magnetic localization; | *interictal MEG gives important information for presurgical evaluation in such cases, especially concerning quantitative correlation of lesion and focal epileptiform activity; further studies with a sufficient number of pts comparing localization interictal and ictal activity are necessary to confirm encouraging results of value of interictal evaluation<br>*using MEG in pts with symptomatic focal epilepsy and lesions may in future help to more precisely plan surgery strategy and reduce amount of removed tissue; MEG helps to reduce need for ECoG |
| (91)<br>Smith et al., 1994<br>Presumed prospective study (not clear from the paper) | *MSI performed for location of seizure focus in surgical candidates (clinical-EEG and/or MRI )<br>*study was to determine to what extent MSI was of assistance in defining the seizure focus in surgical candidates<br>*_no randomization; insufficient description of pt population; no controls; inclusion/exclusion criteria not defined; study not blind and independent; reproducibility not assessed_ | *n=30 pts (21 had previous depth EEG, with ictal data in 12; of 9 who had no invasive EEG, ictal localizing EEG in 4 anteromesial and in 2 lateral temporal cases); all pts on antiepileptic drugs<br>* MEG (37-channel *Biomagnetic Technologies* system; single ECD), with or without EEG triggering; MEG data transformed to MRI images (1.5T) for source localization | *MSI localizing data in 16/30 pts (additional localizing data in 11 lateral focus XMT pts; verifying data in 5 MT pts); MSI convergent enough with clinical-EEG data to obviate invasive studies in 4 XMT pts<br>*MSI no localizing data in 14 pts: 7 had non-localizing EEG or depth/epidural EEG data; 3 had orbitofrontal focus; 1 pt anterior temporal orbitofrontal focus; 1 pt frontal mass (EEG unlocalized); 2 pts anteromesial temporal foci<br>*10 pts with MEG localizing data had surgery (preresection ECoG confirmed): 7/10 seizure-free, 1 rare seizures, 2 < 90% decrease of seizure frequency; | *lack of MSI localization in the case of the orbitofrontal foci suggests the relative insensitivity of MEG to deeper foci which has been previously documented<br>*main advantage of MEG in this study was enhanced spatial definition of convexity interictal epileptiform activity.<br>*this preliminary study suggests that MSI may be a useful non-invasive adjunctive test in evaluating ablative epilepsy surgery candidates<br>*further studies, including longer-term follow-up of surgical cases, are needed |

## Table 5: Studies on the use of MEG for epilepsy (continued)

| Study/design | Role of MEG/ Methodological flaws | Patients' characteristics/Techniques | Results | Conclusions |
|---|---|---|---|---|
| (92)<br>Smith et al. , 1995<br>Presumed prospective study (not clear from the paper) | *MEG was used to evaluate 40 candidates for seizure surgery (thought to have foci outside AMT lobe, based on MRI, scalp-sphenoidal EEG, and/or monitoring with stereotactic depth/epidural/subdural EEG)<br>*the purpose of this study was to determine to what extent 37- or 74-channel MEG was of assistance in defining the interictal epileptic zone in ablative surgery candidates<br>**no randomization; insufficient description of pt population; no controls; inclusion/exclusion criteria not defined; study not blind and independent; reproducibility not assessed* | *n=40 pts (thought to have XTM foci); all pts were on anti-epileptic drugs<br>*pts divided in : n1=29 pts convexity foci; n2=11 pts (3/11 orbitofrontal foci, 1/11orbitofrontal anteriomesial temporal foci)<br>*MEG (single/dual 37-channel *Biomagnetic Technologies* system ; single ECD; interactive software fiducial points to define MEG coordinates on appropriate MRI sections (1.5T); MEG spikes correlated with previous scalp-sphenoidal and depth/epidural/subdural EEG data. In cases not ictally localized, MEG compared to interictal EEG<br>*mean follow-up is 14.2 months | *in n1 MEG spikes recorded in 28/29; in 21/28 MEG and EEG localized to same area; invasive EEG were (7pts), or could be (6pts), avoided based on MEG and non-invasive EEG (54% of 24 non-lesional convexity foci pts);<br>*MEG spikes in 36/40 (90%); not of localizing value in 4 orbitofrontal or 7-depth-non-licalized pts ; 31/36 pts had sufficient MEG data; agreement in 71%, partial agreement in 26%, disagreement in 3%)<br>*17 pts with sufficient MEG data had surgery (16 from n1 and 1 orbitofrontal); EEG and MEG agreement in 13/17; 8/13 seizure free; 1/13 rare seizures, 3/13 have >= 90% seizure frequency reduction, 1/13 has <90% decrease; 4/17 with spatial discordance of MEG and EEG(none is seizure free.; orbitofrontal pt has >=90% seizure frequency reduction) | *lack of MEG localization in orbitfrontal cases may reflect a lessened sensitivity of MEG to deeper foci<br>*in cases with depth/epidural non-localizing EEG data little or no MEG activity, or else multifocal activity was observed in 5/7 cases, suggesting the current limited value of MEG in planning of surgical interventions in such cases<br>*MEG data provided the most useful localizing information in convexity foci cases. Surgical outcome was superior in cases with agreement on EEG and MEG data. Invasive monitoring was or could have been avoided in over 50% of the convexity foci cases<br>Although MEG is not a sand alone technology it may be of use in planning and prognosticating the outcome of ablative epilepsy surgery in many XMT cases |
| (93)<br>Smith et al., 1995<br>Presumed prospective study (not clear from paper) | *MEG used to evaluate pts referred for ablative epilepsy surgery<br>*post-operative follow-up 3-23 months<br>**no randomization; insufficient description of pt population; inclusion/exclusion criteria not clearly defined; study not blind and independent; reproducibility not assessed;* | n=50 pts; all had antiepileptic drugs; no invasive EEG activation performed<br>*pts divided in: n1=20 with suspected convexity foci (interictal/ictal EEG in 19); n2=18 with AMT foci; n3=4 with orbitofrontal foci (ictal depth);<br>*n4= 6 previous convexity cases (historical controls, no MEG) comparable with 8 non-lesional convexity pts; (1 -year follow-up)<br>*MEG at one of 2 sites (single- and dual-probe *Biomagnetic Technologies* systems ; single ECD); after MEG, a multiplanar T1- and T2-weighted image sequences (GE Signa 1.5-T or Siemens Magnetom 1.5 T scanner); MEG data correlated with previous scalp and depth EEG ictal data | *MEG spikes in 42 pts (84%);adequate MEG in 78% of pts (39/50); agreement with EEG in 28/39 (72%), disagreement in 5/39 (13%), partial agreement in 6/39 (15%)<br>*in n1, MEG data in 19 pts (Se of 95%); EEG agreement in 16/19 (11/16 are >=90% improved after surgery)<br>*in n2, 10/18 ictal scalp EEG (MEG agreement in 6/10; no MEG in 4); 8/18 depth EEG (MEG agreement in 4, partial agreement in 2, disagreement in 2); 15 pts had surgery; MEG agreement with scalp+depth EEG in 8/15; (5 seizure-free, 3 rare seizures); 4/15 with no MSI data (3 seizure free, 1 rare seizures); 1 pt with partial agreement is seizure free; 2 pts with disagreement are seizure free;<br>*in n3, no MEG data in 1, anterior temporal MEG dipoles in 1 (disagreement) ; 1 rare temporal dipoles MEG (disagreement); 1pt with bilateral postcentral MEG (disagreement); all had surgery (2 seizure free; 1 rare seizures; 1>=90% decrease in seizure frequency) | *based on MSI and non-invasive EEG data invasive studies were bypassed in 7/17 cases (41%); invasive studies could have been bypassed in another 4/17 cases (24%)<br>*agreement of MEG and EEG in 19 pts who had surgery: 14 seizure-free, 3 had rare seizures, 2 had a >=90% decrease in seizure frequency<br>*in n1 invasive studies avoided in 6/8 non-lesional convexity pts and could have been avoided in another one based on agreement between MEG and EEG<br>*there appeared to be a close spatial correlation between the location of interictal ECoG and MEG data in AMT cases with anterotemporal MEG spike dipoles |

# References


1. Aine CJ. A conceptual overview and critique of functional neuroimaging techniques in humans: I. MRI/FMRI and PET. *Critical Reviews in Neurobiology* 1995;9:229-309.

2. Aung M, Sobel DF, Gallen CC, et al. Potential contribution of bilateral magnetic source imaging to the evaluation of epilepsy surgery candidates. *Neurosurgery* 1995;37:1113-1121.

3. Australian Health Ministers' Advisory Council, Superspecialty Services Subcommittee. *Guidelines for comprehensive epilepsy centres*. Canberra, Australian Government Printing Service 1990.

4. Australian Healthcare Associates. *Review of the current status of the clinical use of magnetic resonance imaging.* Melbourne 1996.

5. Australian Institute of Health & Welfare. *Magnetoencephalography (MEG), Emerging Health Technology Brief.* Canberra, 1992.

6. Beisteiner R, Gomiscek G, Erdler M, et al. Comparing localization of conventional functional magnetic resonance imaging and magnetoencephalography. *European Journal of Neuroscience* 1995;7:1121-1124.

7. Benbadis SR, So NK, Antar MA, et al. The value of PET scan (and MRI and Wada test) in patients with bitemporal epileptiform abnormalities. *Archives of Neurology* 1995;52:1062-1068.

8. Bookheimer SY. Functional MRI applications in clinical epilepsy. *Neuroimage* 1996;4:S139-S146

9. British Epilepsy Association. Epilepsy means a tendency to have recurrent seizures. http://www.folly.co.uk/aura/epilepsy.htm . 1998.

10. Brunetti A, Alfano B, Soricelli A, et al. Functional characterization of brain tumors: an overview of the potential clinical value. *Nuclear Medicine & Biology* 1996;23:699-715.

11. Cendes F, Andermann F, Dubeau F, et al. Proton magnetic resonance spectroscopic images and MRI volumetric studies for lateralization of temporal lobe epilepsy. *Magnetic Resonance Imaging* 1995;13:1187-1191.

12. Cendes F, Caramanos Z, Andermann F, et al. Proton magnetic resonance spectroscopic imaging and magnetic resonance imaging volumetry in the lateralization of temporal lobe epilepsy: a series of 100 patients. *Annals of Neurology* 1997;42:737-746.

13. Chee MW, Morris HH, Antar MA, et al. Presurgical evaluation of temporal lobe epilepsy using interictal temporal spikes and positron emission tomography. *Archives of Neurology* 1993;50:45-48.

14. Chiron C, Syrota A. [Brain functional imaging in children. Progresses and perspectives] [French]. *Archives de Pediatrie* 1995;2:111-115.

15. Chuang SH, Otsubo H, Hwang P, et al. Pediatric magnetic source imaging. *Neuroimaging Clinics of North America* 1995;5:289-303.

16. Chugani HT. The role of PET in childhood epilepsy. *Journal of Child Neurology* 1994;9 Suppl 1:S82-S88

17. Chugani HT, Shewmon DA, Shields WD, et al. Surgery for intractable infantile spasms: neuroimaging perspectives. *Epilepsia* 1993;34:764-771.

18. Cohen MS, Bookheimer SY. Loalization of brain function using magnetic resonance imaging. *Trends in Neurosciences* 1994;17:268-277.

19. Connelly A, Jackson GD, Duncan JS, et al. Magnetic resonance spectroscopy in temporal lobe epilepsy. *Neurology* 1994;44:1411-1417.

20. Conseil d'evaluation des technologies de la sante du Quebec. *Magnetic resonance spectroscopy, Technology Brief.* 9-15-1997. Montreal, CETS

21. Constantinidis I, Malko JA, Peterman SB, et al. Evaluation of 1H magnetic resonance spectroscopic imaging as a diagnostic tool for the lateralization of epileptogenic seizure foci. *British Journal of Radiology* 1996;69:15-24.

22. Cook MJ, Kilpatrick C. Imaging in epilepsy. *Current Opinion in Neurology* 1994;7:123-130.

23. Cross JH, Connelly A, Jackson GD, et al. Proton magnetic resonance spectroscopy in children with temporal lobe epilepsy. *Annals of Neurology* 1996;39:107-113.

24. Cross JH, Gordon I, Connelly A, et al. Interictal 99Tc(m) HMPAO SPECT and 1H MRS in children with temporal lobe epilepsy. *Epilepsia* 1997;38:338-345.

25. Delbeke D, Lawrence SK, Abou-Khalil BW, et al. Postsurgical outcome of patients with uncontrolled complex partial seizures and temporal lobe hypometabolism on 18FDG-positron emission tomography. *Investigative Radiology* 1996;31:261-266.

26. Duncan JS. Magnetic resonance spectroscopy. *Epilepsia* 1996;37:598-605.

27. Duncan JS. Imaging and epilepsy. *Brain* 1997;120:339-377.

28. Ebersole JS, Squires KC, Eliashiv SD, et al. Applications of magnetic source imaging in evaluation of candidates for epilepsy surgery. *Neuroimaging Clinics of North America* 1995;5:267-288.

29. Ende GR, Laxer KD, Knowlton RC, et al. Temporal lobe epilepsy: bilateral hippocampal metabolite changes revealed at proton MR spectroscopic imaging. *Radiology* 1997;202:809-817.

30. Epilepsy Foundation of America. Epilepsy facts and figures. http://www.efa.org/what/education/FACTS.html . 1998.

31. Fineberg HV, Bauman R, Sosman M. Computerized cranial tomography. Effect on diagnostic and therapeutic plans. *Journal of the American Medical Association* 1977;238:224-227.

32. Fois A, Farnetani MA, Balestri P, et al. EEG, PET, SPET and MRI in intractable childhood epilepsies: possible surgical correlations. *Childs Nervous System* 1995;11:672-678.

33. Fried I. Magnetic resonance imaging and epilepsy: neurosurgical decision making. *Magnetic Resonance Imaging* 1995;13:1163-1170.

34. Gadian DG, Connelly A, Duncan JS, et al. 1H magnetic resonance spectroscopy in the investigation of intractable epilepsy. *Acta Neurologica Scandinavica* 1994;Suppl. 152:116-121.

35. Gaillard WD, Bhatia S, Bookheimer SY, et al. FDG-PET and volumetric MRI in the evaluation of patients with partial epilepsy. *Neurology* 1995;45:123-126.

36. Gaillard WD, White S, Malow B, et al. FDG-PET in children and adolescents with partial seizures: role in epilepsy surgery evaluation. *Epilepsy Research* 1995;20:77-84.

37. Gallen CC, Hirschkoff EC, Buchanan DS. Magnetoencephalography and magnetic source imaging. Capabilities and limitations. *Neuroimaging Clinics of North America* 1995;5:227-249.

38. Gallen CC, Schwartz B, Rieke K, et al. Intrasubject reliability and validity of somatosensory source localization using a large array biomagnetometer. *Electroencephalography & Clinical Neurophysiology* 1994;90:145-156.

39. Garcia PA, Laxer KD. Magnetic resonance spectroscopy. *Neuroimaging Clinics of North America* 1995;5:675-682.

40. Garcia PA, Laxer KD, Ng T. Application of spectroscopic imaging in epilepsy. *Magnetic Resonance Imaging* 1995;13:1181-1185.

41. George JS, Aine CJ, Mosher JC, et al. Mapping function in the human brain with magnetoencephalography, anatomical magnetic resonance imaging, and functional magnetic resonance imaging. *Journal of Clinical Neurophysiology* 1995;12:406-431.

42. Guy CN, Walker S, Alarcon G, et al. MEG and EEG in epilepsy: is there a difference? *Physiological Measurement* 1993;14 Suppl. 4A:A99-102.

43. Hamalainen MS. Magnetoencephalography: a tool for functional brain imaging. *Brain Topography* 1992;5:95-102.

44. Heinz R, Ferris N, Lee EK, et al. MR and positron emission tomography in the diagnosis of surgically correctable temporal lobe epilepsy. *American Journal of Neuroradiology* 1994;15:1341-1348.

45. Heiss WD. Positron emission tomography: present and future. *Technology & Health Care* 1996;4:15-29.

46. Helveston W, Gilmore R, Roper S, et al. Intractable temporal lobe epilepsy: comparison of positron emission tomography with qualitative and quantitative MR. *American Journal of Neuroradiology* 1996;17:1515-1521.

47. Henry TR, Engel J Jr, Mazziotta JC. Clinical evaluation of interictal fluorine-18-fluorodeoxyglucose PET in partial epilepsy. *Journal of Nuclear Medicine* 1993;34:1892-1898.

48. Humberstone MR, Sawle GV. Functional magnetic resonance imaging in clinical neurology. *European Neurology* 1996;36:117-124.

49. Ioannides AA, Hellstrand E, Abraham-Fuchs K. Point and distributed current density analysis of interictal epileptic activity recorded by magnetoencephalography. *Physiological Measurement* 1993;14:121-130.

50. Jackson GD. New techniques in magnetic resonance and epilepsy. *Epilepsia* 1994;35 Suppl 6:S2-13.

51. Kelly EF. Noninvasive somatosensory monitoring of the injured inferior alveolar nerve using magnetic source imaging (Discussion). *Journal of Oral and Maxillofacial Surgery* 1996;54:1072-1074.

52. Knowlton RC, Laxer KD, Ende G, et al. Presurgical multimodality neuroimaging in electroencephalographic lateralized temporal lobe epilepsy. *Annals of Neurology* 1997;42:829-837.

53. Kucharczyk J, Anson J, Benzel E, et al. Evaluation of magnetic source imaging for presurgical mapping of brain neoplasms: a two-center retrospective technology assessment study. *Academic Radiology* 1996;3 Suppl. 1:S131-S134

54. Kuzniecky R. Magnetic resonance and functional magnetic resonance imaging: tools for the study of human epilepsy. *Current Opinion in Neurology* 1997;10:88-91.

55. Kuzniecky RI. Neuroimaging in pediatric epilepsy. *Epilepsia* 1996;37 Suppl 1:S10-S21

56. Kwong KK. Functional magnetic resonance imaging with echo planar imaging. *Magnetic Resonance Quarterly* 1995;11:1-20.

57. Langevin F, Vachey C. [Imaging of cerebral function: new trends in PET, MEG and MRI.] [French]. *Journal de Radiologie* 1995;76:45-48.

58. Latchaw RE, Hu X. Functional MR imaging in the evaluation of the patient with epilepsy. Functional localization. *Neuroimaging Clinics of North America* 1995;5:683-693.

59. Laxer KD. Clinical applications of magnetic resonance spectroscopy. *Epilepsia* 1997;38 Suppl 4:S13-S17

60. Laxer KD, Garcia PA. Imaging criteria to identify the epileptic focus. Magnetic resonance imaging, magnetic resonance spectroscopy, positron emission tomography

scanning, and single photon emission computed tomography. *Neurosurgery Clinics of North America* 1993;4:199-209.

61. Le Bihan D. Functional MRI of the brain principles, applications and limitations. *Journal of Neuroradiology* 1996;23:1-5.

62. Lee CC, Jack CRJ, Riederer SJ. Use of functional magnetic resonance imaging. *Neurosurgery Clinics of North America* 1996;7:665-683.

63. Lewine JD, Orrison WW, Jr. Spike and slow wave localization by magnetoencephalography. *Neuroimaging Clinics of North America* 1995;5:575-596.

64. Lounasmaa OV, Hamalainen M, Hari R, et al. Information processing in the human brain: magnetoencephalographic approach. *Proceedings of the National Academy of Sciences of the United States of America* 1996;93:8809-8815.

65. Lu D, Margouleff C, Rubin E, et al. Temporal lobe epilepsy: correlation of proton magnetic resonance spectroscopy and 18F-fluorodeoxyglucose positron emission tomography. *Magnetic Resonance in Medicine* 1997;37:18-23.

66. Lucignani G, Tassi L, Fazio F, et al. Double-blind stereo-EEG and FDG PET study in severe partial epilepsies: are the electric and metabolic findings related? *European Journal of Nuclear Medicine* 1996;23:1498-1507.

67. Maclin EL, Rose DF, Knight JE, et al. Somatosensory evoked magnetic fields in patients with stroke. *Electroencephalography & Clinical Neurophysiology* 1994;91:468-475.

68. Markand ON, Salanova V, Worth R, et al. Comparative study of interictal PET and ictal SPECT in complex partial seizures. *Acta Neurologica Scandinavica* 1997;95:129-136.

69. Mastin ST, Drane WE, Gilmore RL, et al. Prospective localization of epileptogenic foci: comparison of PET and SPECT with site of surgery and clinical outcome. *Radiology* 1996;199:375-380.

70. Masuoka LK, Spencer SS. Clinical neurophysiology in epilepsy. *Current Opinion in Neurology* 1994;7:148-152.

71. Mauguiere F. A consensus statement on relative merits of EEG and MEG. European Concerted Action on Biomagnetism, Lyon meeting, November 26 and 27, 1991. *Electroencephalography & Clinical Neurophysiology* 1992;82:317-319.

72. Mauguiere F, Ryvlin P. [Morphological and functional neuro-imaging of surgical partial epilepsies in adults]. [French]. *Revue Neurologique* 1996;152:501-516.

73. Menzel C, Grunwald F, Shih WJ, et al. 18F-DG PET and RCBF SPECT in epilepsy. *Radiologia Diagnostica* 1994;35:307-314.

74. Messa C, Grana C, Lucignani G, et al. Functional imaging using PET and SPECT in pediatric neurology. *Journal of Nuclear Biology & Medicine* 1994;38:85-88.

75. Moseley ME, Glover GH. Functional MR imaging. Capabilities and limitations. *Neuroimaging Clinics of North America* 1995;5:161-191.

76. Naatanen R, Ilmoniemi RJ, Alho K. Magnetoencephalography in studies of human cognitive brain function. *Trends in Neurosciences* 1994;17:389-395.

77. Nakasato N, Levesque MF, Barth DS, et al. Comparisons of MEG, EEG, and ECoG source localization in neocortical partial epilepsy in humans. *Electroencephalography & Clinical Neurophysiology* 1994;91:171-178.

78. National Health Technology Advisory Panel. *In vivo NMR spectroscopy*. Canberra, Australia 1985.

79. Ng TC, Comair YG, Xue M, et al. Temporal lobe epilepsy: presurgical localization with proton chemical shift imaging. *Radiology* 1994;193:465-472.

80. Novotny EJ, Jr. Overview--the role of NMR spectroscopy in epilepsy. *Magnetic Resonance Imaging* 1995;13:1171-1173.

81. Orrison WW, Jr. 3M Mayneord Memorial Lecture: functional brain imaging--an overview. *British Journal of Radiology* 1996;69:493-501.

82. Prichard JW. New nuclear magnetic resonance data in epilepsy. *Current Opinion in Neurology* 1997;10:98-102.

83. Puce A. Comparative assessment of sensorimotor function using functional magnetic resonance imaging and electrophysiological methods. *Journal of Clinical Neurophysiology* 1995;12:450-459.

84. Radtke RA, Hanson MW, Hoffman JM, et al. Positron emission tomography: comparison of clinical utility in temporal lobe and extratemporal epilepsy. *Journal of Epilepsy* 1994;7:27-33.

85. Rezai AR, Hund M, Kronberg E, et al. The interactive use of magnetoencephalography in stereotactic image-guided neurosurgery. *Neurosurgery* 1996;39:92-102.

86. Roberts T, Rowley H, Kucharczyk J. Applications of magnetic source imaging to presurgical brain mapping. *Neuroimaging Clinics of North America* 1995;5:251-266.

87. Rowley HA, Roberts TP. Functional localization by magnetoencephalography. *Neuroimaging Clinics of North America* 1995;5:695-710.

88. Sankar R, Chugani HT. Strategies for diagnosis and treatment of childhood epilepsy. *Current Opinion in Neurology & Neurosurgery* 1993;6:398-402.

89. Sato S, Malow BA. Electroencephalography and magnetoencephalography in epilepsy and nonepileptic disorders. *Current Opinion in Neurology* 1993;6:708-714.

90. Singh KD. Functional imaging of the brain using superconducting magnetometry. *Endeavour* 1995;19:39-44.

91. Smith JR, Gallen C, Orrison W, et al. Role of multichannel magnetoencephalography in the evaluation of ablative seizure surgery candidates. *Stereotactic & Functional Neurosurgery* 1994;62:238-244.

92. Smith JR, Schwartz BJ, Gallen C, et al. Multichannel magnetoencephalography in ablative seizure surgery outside the anteromesial temporal lobe. *Stereotactic & Functional Neurosurgery* 1995;65:81-85.

93. Smith JR, Schwartz BJ, Gallen C, et al. Utilization of multichannel magnetoencephalography in the guidance of ablative seizure surgery. *Journal of Epilepsy* 1995;8:119-130.

94. Spencer SS. The relative contributions of MRI, SPECT, and PET imaging in epilepsy. *Epilepsia* 1994;35 Suppl 6:S72-S89

95. Spencer SS, Theodore WH, Berkovic SF. Clinical applications: MRI, SPECT, and PET. *Magnetic Resonance Imaging* 1995;13:1119-1124.

96. Spitzer M, Kammer T. Combining neuroscience research methods in psychopathology. *Current Opinion in Psychiatry* 1996;9:352-363.

97. Stefan H. Clinical applications of MEG in epilepsy. *Brain Topography* 1993;5:425-427.

98. Stefan H, Schneider S, Feistel H, et al. Ictal and interictal activity in partial epilepsy recorded with multichannel magnetoelectroencephalography: correlation of electroencephalography/electrocorticography, magnetic resonance imaging, single photon emission computed tomography, and positron emission tomography findings. *Epilepsia* 1992;33:874-887.

99. Stefan H, Schuler P, Abraham-Fuchs K, et al. Magnetic source localization and morphological changes in temporal lobe epilepsy: Comparison of MEG/EEG, ECoG and volumetric MRI in presurgical evaluation of operated patients. *Acta Neurologica Scandinavica* 1994;Suppl. 89:83-88.

100. Theodore WH. Positron emission tomography and single photon emission computed tomography. *Current Opinion in Neurology* 1996;9:89-92.

101. Theodore WH, Gaillard WD, Sato S, et al. Positron emission tomographic measurement of cerebral blood flow and temporal lobectomy. *Annals of Neurology* 1994;36:241-244.

102. Theodore WH, Sato S, Kufta CV, et al. FDG-positron emission tomography and invasive EEG: seizure focus detection and surgical outcome. *Epilepsia* 1997;38:81-86.

103. Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: Magnetoencephalography (MEG). *Neurology* 1992;42:1-4.

104. Valk PE, Laxer KD, Barbaro NM, et al. High-resolution (2.6-mm) PET in partial complex epilepsy associated with mesial temporal sclerosis. *Radiology* 1993;186:55-58.

105. Weisskoff RM. Functional MRI: are we all moving towards artifactual conclusions? Or fMRI fact or fancy?. *NMR in Biomedicine* 1995;8:101-103.

106. Wieser HG. PET and SPECT in epilepsy. *European Neurology* 1994;34 Suppl. 1:58-62.

107. Wiskwo JJ, Gevins A, Williamson SJ. The future of the EEG and MEG. *Electroencephalography & Clinical Neurophysiology* 1993;87:1-9.

108. Yue NC. Advances in brain tumor imaging. *Current Opinion in Neurology* 1993;6:831-840.

109. Zupanc ML. Neuroimaging in the evaluation of children and adolescents with intractable epilepsy: II. Neuroimaging and pediatric epilepsy surgery. *Pediatric Neurology* 1997;17:111-121.